Clinical Trials Regulations (CTR) –

An analysis of the first clinical trial applications in the public portal of the Clinical Trials Information System (CTIS)

Masterarbeit

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List of Abbreviations

AI	Artificial Intelligence
AR	Assessment Report
AT	Austria
BE	Belgium
BG	Bulgaria
CTAG	Clinical Trials Coordination and Advisory Group
CTD	Clinical Trials Directive
CTIS	Clinical Trials Information System
CTR	Clinical Trials Regulation
CZ	Czechia
DE	Germany
DK	Denmark
DMC	Data Monitoring Committee
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
ES	Spain
EU	European Union
FI	Finland
FR	France
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GR	Greece
HR	Croatia
HU	Hungary
IB	Investigators Brochure
IE	Ireland
ICF	Informed Consent Form
IS	Iceland
IT	Italy

IMPD	Investigator Medicinal Product Dossier
LV	Latvia
MSC	Member State Concerned
NL	Netherlands
NO	Norway
PL	Poland
PT	Portugal
RFI	Request for information
RMS	Reporting Member State
RO	Romania
SE	Sweden
SI	Slovenia
SK	Slovakia

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1. Introduction

"*Doctors and ethicists fear chaos in clinical trials*" – this was the headline of an article in a well-known German newspaper by the end of the year 2022 (1). Background to this radical statement were problems with the use of a new electronical portal, the "Clinical Trials Information System" (CTIS). CTIS is a portal linked to a database, which is "*the single entry point for clinical trials information in the European Union (EU) and in the European Economic Area (EEA)*" since 31st January 2022 (2). Functionality of CTIS was the prerequisite for the Regulation (EU) No 536/2014, also known as the Clinical Trials Regulation (CTR), to become applicable within the EU[1], as laid out in articles 80 and 81 of the CTR (3).

The CTR came into force on 16th June 2014 already and repeals the former legal basis, the Directive 2001/20/EC, known as the "Clinical Trial Directive" (CTD), since it came into effect in January 2022 (4,5). Along with the CTR major changes in the regulatory environment for clinical trials in the EU were introduced. The aim of the CTR is to harmonize the regulatory processes and to speed up the authorization process of clinical trials within the EU. Moreover, it aims to simplify the application processes for clinical trials for sponsors, to increase the number of trials running in the EU. In addition, more transparency on clinical trials data is aimed to be achieved with the legal framework of the CTR (3–5).

In the first year after the CTR came into effect, the submission of initial clinical trial applications was on a voluntary basis. Since 31st January 2023, initial clinical trial applications within the EU must be submitted under the legal framework of the CTR (4,5). All ongoing clinical trials authorized under the legal framework of the CTD with at least one active site within the EU on 30th January 2025 also need to be transitioned from the CTD to the CTR. Sponsors need to submit a transitioning application in CTIS for all concerned clinical trials. Based on the latest specifications, this is considered an administrative process, following a minimum approach to comply with the requirements of the CTR (6).

[1] EU should be read as EU/EEA in the following, as the CTR is also applicable for clinical trials in the EEA

Initial clinical trial applications consist of a common part for all member states (Part I) and a member state specific part (Part II). Only one initial clinical trial application including all member states concerned (MSC) is performed by the sponsor via CTIS. After successful validation of the submitted initial clinical trial application, Part I and Part II assessments take place in parallel. Part I of the initial clinical trial application is assessed by the national competent health authorities of each MSC, coordinated by a Reporting Member State (RMS) in case of multinational trials. The RMS issues the conclusion for the part I assessment, which is also applicable for all involved MSC. In case a MSC disagrees with the conclusion on Part I of the RMS, it has the authority to issue a disagreement and refuse to authorize the conduct of the clinical trial in its territory (3,7).

Part II is assessed by one or more national ethics committees of the MSC. Questions or requests from the MSC during validation or assessment phase to the sponsor are raised in a request for information (RFI). After notifying the sponsor of part I and part II conclusions, each MSC informs the sponsor whether the clinical trial application has been authorized. Potential outcomes for an initial clinical trial application include authorization, authorization with conditions, or non-authorization of the trial (3,7).

The following standard timelines for these steps in the authorization of an initial clinical trial application apply (3,7): Validation: 10 to 25 days (without and with RFI); Assessment Part I and Part II: 45 to 76 days (without and with RFI); Decision: 5 days. According to article 18 (5) of the CTR, Part I Assessment can be extended up to 50 additional days, in case the trial is including an Advanced Therapy Medicinal Product and consultation of experts is needed (3).

Exceeding the maximum timelines by the MSC can result in tacit decision for Part I or Part II assessment as set in article 8 (6) of the CTR (3). If the sponsor is exceeding the maximum timelines for the response to a RFI this leads to the lapse of the clinical trial application (3,7).

Initial clinical trial applications can either be performed as full initial clinical trial application including Part I and Part II at the same time, or partial initial clinical trial application including Part I for all MSC and Part II only for some or none MSC. In case of a partial initial clinical trial

application, Part II must be submitted to the remaining MSC within two years after decision for Part I (3,7).

One part of CTIS is a public portal, a website online where information regarding clinical trials within the EU is publicly accessible. The public CTIS portal goes along with the aim of the CTR to provide more transparency about clinical trials within the EU to the public, as laid out in recital number 67 of the CTR (3,4,8). According to article 81(4) of the CTR, all information should be made public, except for personal data, commercially confidential information, confidential communication between member states or information regarding an effective supervision of the conduct of a clinical trial by member states (3). The sponsor can request a deferral of publication of trial documents by the time of the submission of an initial clinical trial application. Once granted, this will lead to a delay of the publication of a certain document on the public CTIS portal (9). The deferral functionality led to a technical issue, which is already known to the EMA. Due to this technical issue, only limited trial applications are published in the public CTIS portal up to now (September 2023) (10).

Despite this current limited availability of published clinical trial applications, the public CTIS portal provides considerably more information about clinical trials within the EU than previously available. This includes detailed timelines of the regulatory process, such as submission date of procedures, receipt date of RFI and sponsor response date to those RFI. Moreover, the questions which are raised from health authorities or ethic committees during validation, Part I or Part II assessment are published in detail. Also, the sponsors response to these questions is visible. Moreover, Part I and Part II assessment reports outlining the details of the assessment are accessible. Among the regulatory documents, numerous clinical trial documents, like clinical trial protocols, Investigator Brochures (IB), Investigator Medicinal Product Dossiers (IMPD) or Informed Consent Forms (ICF) are also published in the public CTIS portal (2).

The newly publicly available information within the public CTIS portal is the basis for this master thesis.

2. Objectives

The overall goal of this master thesis is to find out, what insights can be gained from the first initial clinical trial applications published in the public CTIS portal since its implementation 1.5 years ago. In particular, the following questions are aimed to be answered in to gain new information about the outcomes and timelines of each procedure step in the authorization process of an initial clinical trial application under the legal framework of the CTR:

Validation phase:

1. What was the outcome of the validation regarding the validity of initial clinical trial applications and the frequency of raised RFI?
2. What was the duration of the validation phase from the time of submission of the initial clinical trial application to completion of the validation?

Part I assessment:

1. What was the outcome of the Part I assessment in terms of the authorization or non-authorization of initial clinical trial applications and the frequency of raised RFI?
2. What was the duration of the Part I assessment phase from the validation of the initial clinical trial application?

Part II assessment:

1. What was the outcome of the Part II assessment in terms of the authorization or non-authorization of initial clinical trial applications and the frequency of raised RFI?
2. What was the duration of the Part II assessment phase from the validation of the initial clinical trial application?

Decision:

1. What was the duration from conclusion of Part I or Part II assessment and from the submission of the initial clinical trial application until final decision by each MSC?

These objectives are aimed to be answered through a systematic analysis of all initial clinical trial applications which are available in the public CTIS portal by the end of July 2023. This is intended to provide a comprehensive picture of the first initial clinical trial applications.

3. Material und Methods

3.1. Public CTIS portal

As described before, the basis for this master thesis is the public CTIS portal, available online at www.euclinicaltrials.eu. Each clinical trial application with a final decision under the legal framework of the CTR is intended to be published here according to article 81(4) of the CTR (3).

In the present analysis all clinical trial applications in the public CTIS portal until 31st July 2023 at 12pm were included. This covers the first half year of mandatory use of the CTR from 30th January 2023 to 31st July 2023 as well as the full first year of voluntary use from 31st January 2022 to 29th January 2023 (5).

The website of the public CTIS portal was accessed using Microsoft® Edge® Version 115.0.1901.200. All published clinical trial applications in the public CTIS portal were listed by using the “search clinical trials and reports” and subsequent “search for clinical trials” function. By using the “Download results” function, all included clinical trial applications were exported to a “csv”-file. Before that, all fields within the “display options” were selected, to automatically download all available information for each initial clinical trial application, like therapeutic area, recruitment status and sponsor type. All information about clinical trial applications in the public CTIS portal, which were included in the download from the public CTIS portal are listed in Appendix 1.

Additional parameters have been extracted manually from the public CTIS portal, since the information which are included in the automatically downloaded file are not fully sufficient to answer the research questions. All pre-defined parameters for manual extraction from the

public CTIS portal for each clinical trial application are compiled in Appendix 2. This information for individual clinical trial applications was retrieved by clicking on each entry in the public CTIS portal. On the first page of each clinical trial entry in the public CTIS portal, the summary information is provided, like first submission date, last update date, overall trial status and whether the clinical trial application is concerning a transition trial or not. The next tab in the public CTIS portal is providing full trial information, including trial documents and Part II documents. Information on the authorization process of the initial clinical trial application was collected by clicking on the "Applications" field in this tab and "view details" for the initial application. This leads to a new page on the website, where all Part I and Part II information and corresponding documents, such as RFIs or Part I and Part II assessment reports are displayed, if available.

For the present analysis, all clinical trial applications in the public CTIS portal have been downloaded on 31st July, 2023 at 12pm.

3.2. Database creation

The downloaded clinical trial applications were imported into Microsoft® Excel® for Microsoft 365 MSO (Version 2306 Build 16.0.16529.20226) to create the database. The additional manually extracted parameters for each clinical trial application are supplemented therein. Once all information has been compiled within Microsoft® Excel®, this represents the database, which is the basis for the following analyses.

Analyses were performed in Microsoft® Excel® as well, using formulas and pivot tables. The numbers and proportions of the outcome of each procedure step were compiled using pivot. The analyses of the outcome of each procedure step of the authorization process for initial clinical trial applications and the creation of the diagrams by MSC were also carried out using Pivot.

Calculations of the timelines for each procedure step were performed in a stepwise approach. Firstly, the raw duration in calendar days was calculated using a formula in Microsoft® Excel®

to subtract one date from the other. Next, it was identified, whether the period falls into the winter clock stop set by the EMA. This clock stop is set by the EMA during winter holiday period from 23th December to 7th January and also affects the calculation of timelines in CTIS. Days which fall in this period do not count to the overall timelines (11). The winter clock stop was taken into account in the analysis by checking, if the first analyzed date was before 23th December 2022 or the last analyzed date after 7th January 2023. If that was the case, 15 days were subtracted from the total duration to correctly reflect the winter clock stop. For example, if validation conclusion date was on 20th December 2022 and Part I conclusion date on January 10th, 2023, the 15 days during winter clock stop did not count to the timelines for Part I assessment. The duration adjusted by winter clock stop was the basis for the subsequent analyses of average, minimum and maximum duration for validation, Part I, Part II assessment and the duration to decision using Pivot. Analyses of timelines by each individual MSC were also performed accordingly.

Further country specific holidays were not taken into consideration. They have been considered negligible due to a similar distribution across the member states (12). Furthermore, due dates falling on weekends were not considered.

Due to the partly small number of initial clinical trial applications per MSC, it was not always possible to calculate an average value for each individual MSC. In this case the actual value for this MSC was presented and compared to the average numbers of other MSC.

Exclusion of specific values which were not plausible had to be excluded from the analysis if no valid explanation could not be found. If exclusion of specific values from the analysis was necessary, was made transparent in the description of the results.

Quality checks were performed after compilation of the database as well as throughout the analysis via regular consistency checks of the data and calculation results. In addition, the extracted information was verified randomly. Furthermore double proofing of calculation results and plausibility checks have been performed for all analyses.

The final database including all corresponding analyses is made publicly available online and can be accessed under the following link: https://doi.org/10.5281/zenodo.8352874 (13).

4. Results

The data cut off on 31st July, 2023 at 12 pm resulted in a total of 200 clinical trial applications in the public CTIS portal (13). Figure 1 shows all identified clinical trial applications in the public CTIS portal by the time of data cut-off.

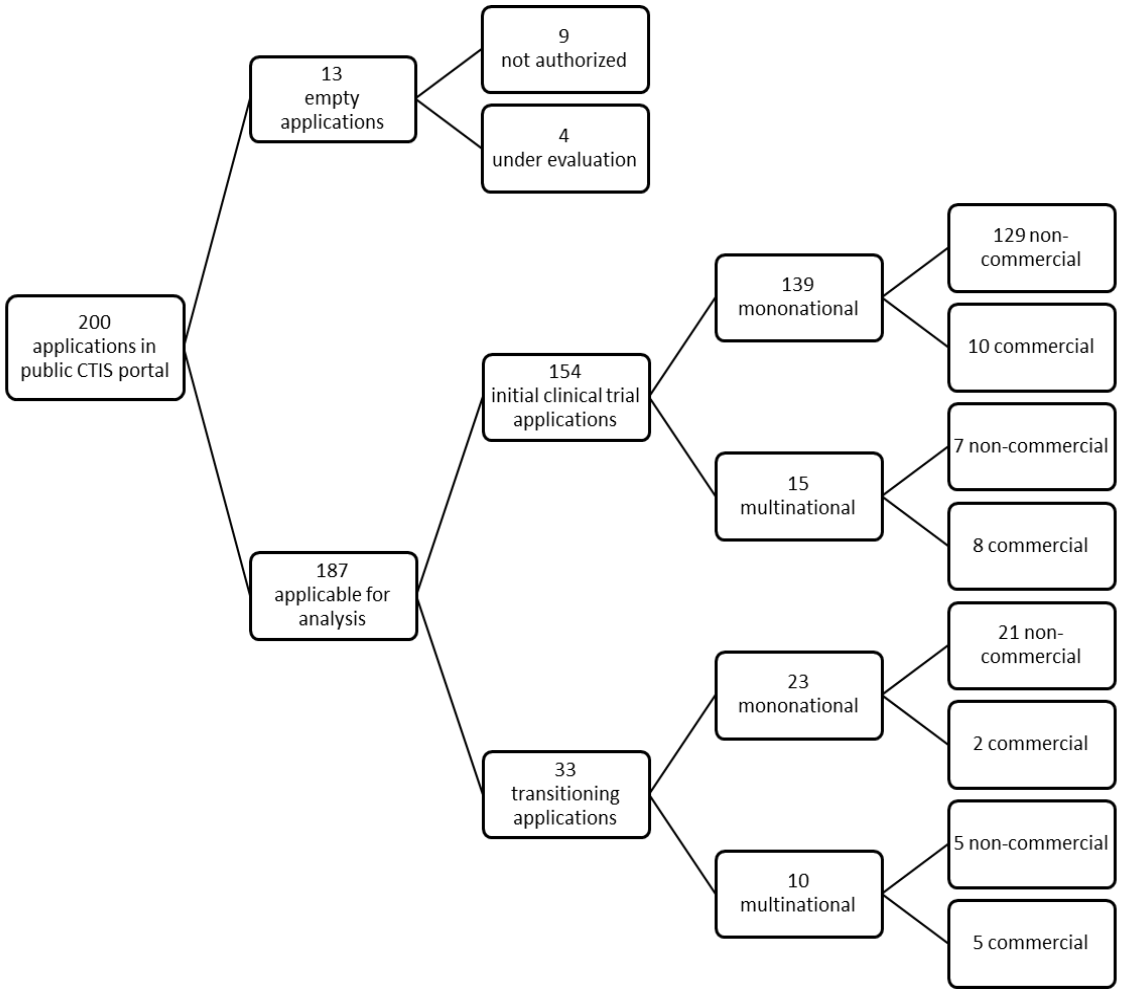

Figure 1: Identified clinical trial applications in the public CTIS portal on 31st July, 2023

CTIS = Clinical Trials Information System

Source: Own calculations based on information from the public CTIS portal (13,14)

Out of the 200 identified clinical trial applications, 187 were applicable for the further analysis, given that further information was provided in the public CTIS portal, which could be used to answer the objectives.

For 13 clinical trial applications only limited information was available, such as trial number, overall trial status and countries where the trial is taking place. Of these, 9 applications were not authorized and 4 applications were still under evaluation by the time of the data cut off (13). It is unclear whether these applications are initial clinical trial applications or transitioning applications. Due to the limited available information, they were not included in the further analysis.

Some EU clinical trial numbers indicated that these initial clinical trial applications were resubmissions, identified by the two end digits other than “00”, e.g. “-01” or “-02”. This indicates the first or second resubmission of the initial clinical trial application.

In total, 33 transitioning applications were identified. 70% (n=23) of them are concerning mononational trials and 30% (n=10) multinational trials. Transitioning applications for mononational trials were submitted mostly from non-commercial sponsors (91%; n=21). Transitioning applications for multinational trials were submitted in equal shares by commercial and non-commercial sponsors with 5 each (50%). Since transitioning applications are not relevant to answer the objectives, they were not included within the further analysis.

There were several substantial and non-substantial modifications listed for the identified trials in the public CTIS portal, ranging up to a maximum of 4 substantial modifications and 6 non-substantial modifications for two mononational trials (2022-500657-17-00; 2022-501329-18-00) (13).

Subsequent applications for the addition of a new MSC were listed for 4 initial clinical trial applications in total, ranging from 1 to 3 additional MSC per trial (13). Initial clinical trial applications, which were initially submitted to one MSC only and subsequently added new MSC after authorization of the initial clinical trial application, were considered as applications for mononational trials for the following analyses.

There was one temporary halt identified for a mononational trial (2022-501559-99-00). This temporary halt was due to feasibility issues because not enough cases of the disease COVID-19 occurred (15). No further exceptional reporting events such as serious breaches,

unexpected events, urgent safety measures or temporary halts were identified in the analysis for the other trials (13).

One trial was listed as already completed (2023-504256-10-00). Recruitment start date for this mononational trial conducted in France was on 10th July 2023 and end date already 5 days later on 15th June 2023 (16). No trial results are available within the public CTIS portal for this trial yet, however the reporting due date was not yet reached.

Among initial clinical trial applications, mononational trials submitted from non-commercial sponsors made up the largest proportion with 84% (n=129). Only 5% (n=8) initial clinical trial applications were concerning multinational trials conducted from commercial sponsors (13). Figure 2 shows the number initial clinical trial applications by MSC for mononational trials included in the analysis.

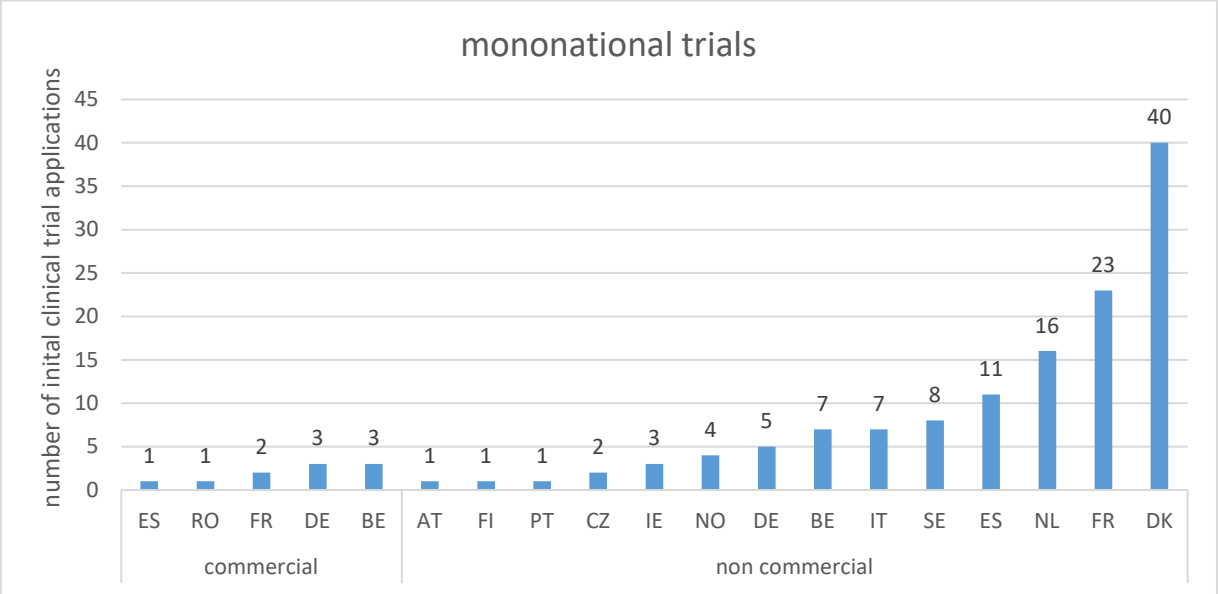

Figure 2: Number of mononational initial clinical trial applications by MSC included in the analysis

Source: Own calculations based on information from the public CTIS portal (13,14)

Most of the mononational initial clinical trial applications were submitted in Denmark with 40 applications in total, counting to 26% of all initial clinical trial applications. All these

applications were submitted from non-commercial sponsors, mainly (university) hospitals. A similar picture emerges for initial clinical trial applications submitted for mononational trials in France and Netherlands (13).

The number of initial clinical trial applications for mononational trials which were submitted from commercial sponsors is significantly smaller than for non-commercial sponsors with only 10 in total. Most of the mononational initial clinical trial applications were submitted from commercial sponsors in Germany and Belgium (n=3), followed by France (n=2) (13).

After outlining the results for mononational initial clinical trial applications, the number of multinational initial clinical trial applications, which are included in the analysis, is illustrated. Figure 3 shows the multinational initial clinical trial applications which were identified in the analysis according to the respective RMS.

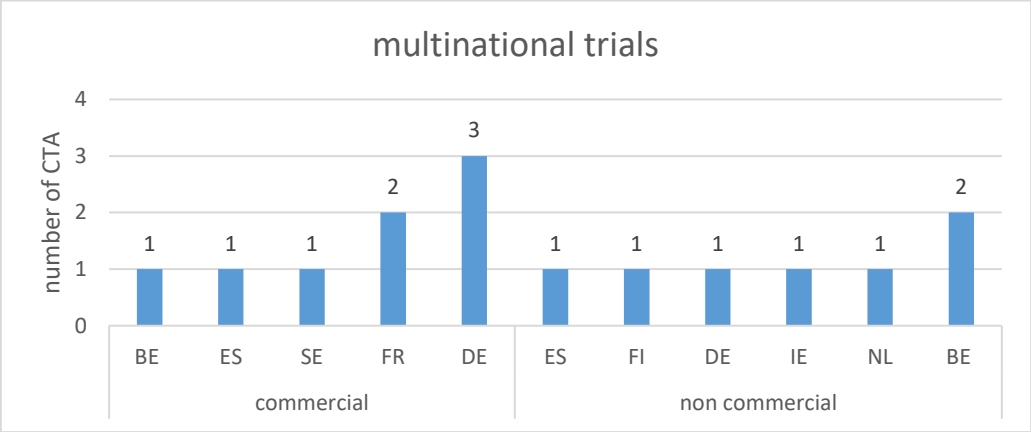

Figure 3: Number of multinational initial clinical trial applications by RMS included in the analysis

Source: Own calculations based on information from the public CTIS portal (13,14)
CTA = Clinical trial application.

The most common RMS for multinational initial clinical trial applications was Germany with 4 procedures in total (3 for commercial trials and 1 for a non-commercial trial), followed by Belgium as RMS for 3 procedures in total (1 commercial trial and 2 for non-commercial trials) and France with 2 procedures in total, both for commercial trials. For all other RMS only one

multinational initial clinical trial application was identified in the analysis. The number of MSC included in these initial clinical trial applications for multinational trials ranged from 2 MSC up to 10 MSC (13).

4.1. Validation of the initial clinical trial application

4.1.1. Outcome of the validation phase

After the submission of an initial clinical trial application in CTIS, the first step in the authorization process under the legal framework of the CTR is the validation of the application.

All initial clinical trial applications, that were included in the analysis, were assessed as valid by the MSC during the validation phase. No invalid initial clinical trial applications were identified (13).

For most of the initial clinical trial applications (84%) at least one validation RFI was published as displayed in Table 1. There was no big difference between mononational and mulitnational or commercial and non-commercial trials (13).

Table 1: Number of initial clinical trial applications with and without an issued validation RFI

	No validation RFI issued	At least one validation RFI issued	Total
mononational	**23 (17%)**	**116 (83%)**	**139**
commercial	4 (40%)	6 (60%)	10
non-commercial	19 (15%)	110 (85%)	129
multinational	**2 (13%)**	**13 (87%)**	**15**
commercial	1 (13%)	7 (88%)	8
non-commercial	1 (14%)	6 (86%)	7
Total	**25 (16%)**	**129 (84%)**	**154**

RFI = Request for information.
Source: Own calculations based on information from the public CTIS portal (13,14)

For those applications which received at least one validation RFI the average number of RFIs is 1.33. The maximum number of RFI issued for one application counts to 4 RFIs. These 4 RFIs were issued from the Dutch health authority for one mononational trial (2023-505317-25-00) (13). The different RFIs were published few days apart from each other and are not related to each other, each covering different validation related topics (17).

4.1.2. Timelines for validation phase

Following the results of the outcomes of the validation phase, the results of the timelines are presented. The average duration from submission of the initial clinical trial application to validation conclusion date was 17 days with a minimum of zero days and a maximum of 42 days. Mononational trials were validated on average 11 days faster than multinational trials as outlined in Table 2.

Two mononational trials were listed with validation and submission on the same day (2022-500377-13-01 & 2022-502621-17-00), and for both no validation RFI was published as well. The maximum duration of 42 days for validation occured for one initial clinical trial application

for a mononational, non-commerical trial conducted in France (2022-502426-41-00), for which 3 validation RFIs were raised in total (13).

Within mononational and multinational initial clinical trial applications there was no significant difference between the average duration from submission to validation conclusion for trials submitted from commercial and non-commercial sponsors.

Table 2: Duration from submission of the initial clinical trial application to validation conclusion

	Average in days	Minimum in days	Maximum in days
mononational	**16**	**0**	**42**
commercial	11	1	26
non-commercial	17	0	42
multinational	**27**	**2**	**32**
commercial	29	26	32
non-commercial	24	2	32
Total	**17**	**0**	**42**
Source: Own calculations based on information from the public CTIS portal (13,14)			

Figure 4 below is outlining the duration from submission to validation conclusion date by MSC for initial clinical trial applications depending to whether a validation RFI was received or not. Due to the partially small number of procedures per MSC, an average value could not always be calculated. In case only one application has been carried out in the individual MSC, the value shown in Figure 4 reflects the actual number of days for this validation procedure.

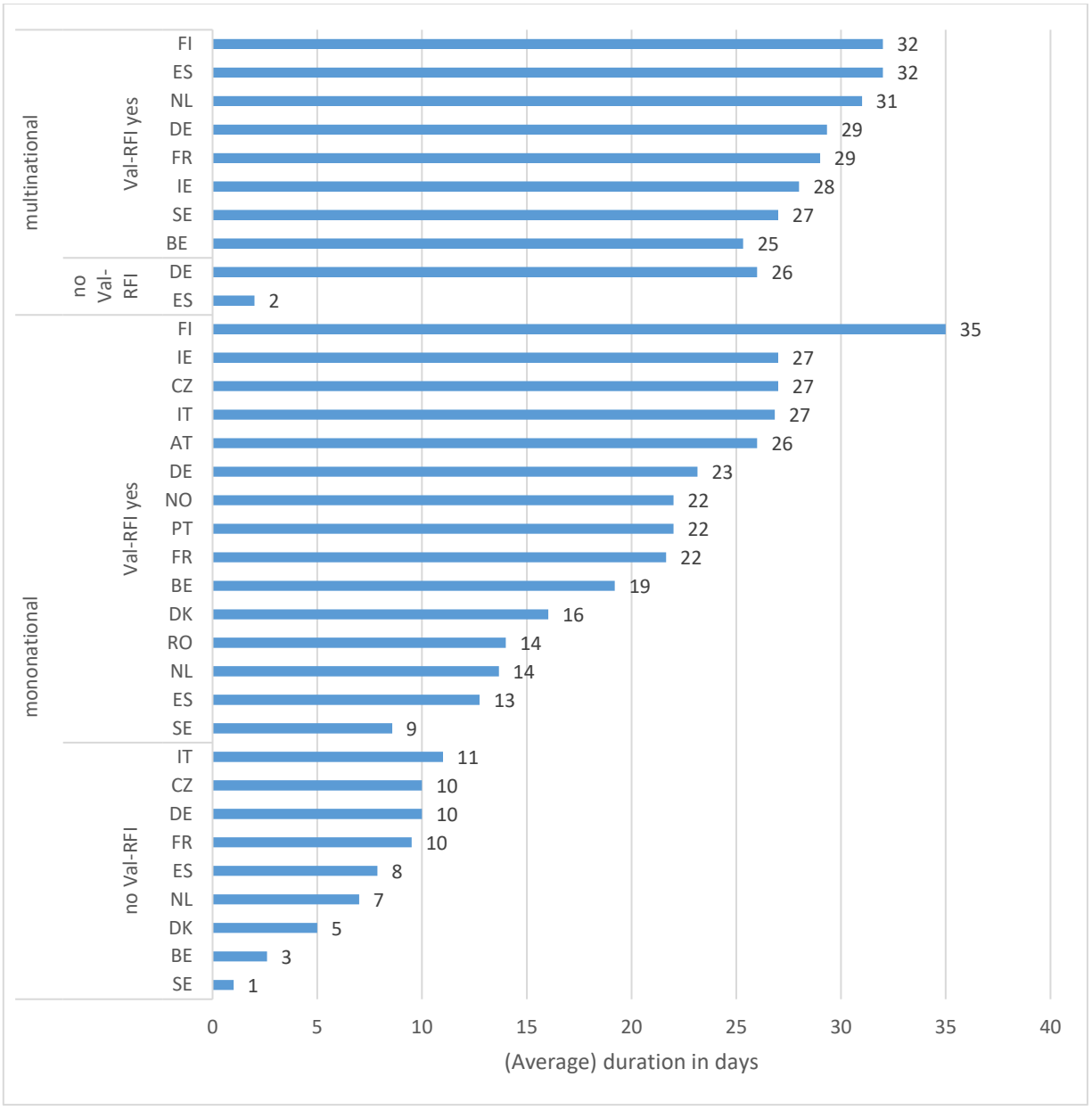

Figure 4: (Average) duration from submission to validation conclusion by MSC (RMS for multinational trials)

Source: Own calculations based on information from the public CTIS portal (13,14)

Particularly for mononational trials, there was a significant difference in the average duration for validation by the individual MSC, if there was at least one validation RFI issued, ranging from 9 days on average for Sweden (n=8) up to 35 days for Finland (n=1). The duration for multinational trials with at least one validation RFI was distributed more evenly, ranging from

25 days for RMS Belgium up to 32 days for RMS Finland and Spain. However, it must be noted that the number of initial clinical trial applications per RMS was mostly only one, as previously shown in Figure 3 (13).

For mononational initial clinical trial applications without any validation RFI, the average duration was ranging from only one to 11 days. Only two multinational applications without any validation RFI during validation were included, one for RMS Spain (2022-501132-42-00) and the other for RMS Germany (2022-500014-26-00). These showed a big difference in their time from submission to validation with 2 days for Spain (n=1) and 26 days for Germany (n=1) (13). However, it was unclear, whether a validation RFI was actually not issued for the validation of the initial clinical trial application from RMS Germany or just not published, since no Part I assessment report was published in the public CTIS portal either (18).

4.2. Part I assessment of the initial clinical trial application

4.2.1. Outcome of Part I assessment

After the validity of the initial clinical trial application is determined, the assessment of Part I and Part II takes place in parallel for full initial clinical trial application. No partial initial clinical trial application was identified in the analysis (13). Therefore, Part I and Part II assessments were running in parallel for all initial clinical trial applications included in the following analyses.

Most of the initial clinical trial applications were fully accepted within the Part I assessment (85%), with a higher rate for mononational trials (87%) in comparison to multinational trials (67%). In total 14% of the initial clinical trial applications were accepted with conditions only trials (13).

One mononational trial conducted in Denmark (2022-503010-23-01) was listed with “no conclusion” for Part I and Part II assessment within the initial application tab in the public CTIS portal. The current status within the summary and decision sheet was listed as “authorized”

(13). This suggests that a tacit approval applied. However, since both assessment conclusions were listed with “no conclusion”, the overall trial status in case of a tacit approval is foreseen to be displayed as “under evaluation” (19). No reason could be found for this deviation.

As shown in Table 3, in total 22 initial clinical trial applications were “acceptable with conditions” for the Part I assessment, 17 for mononational and 5 for multinational trials (13). There are no big differences to be noted between commercial and non-commercial initial clinical trial applications for neither mononational nor multinational clinical trials.

Table 3: Outcome of Part I assessment for initial clinical trial applications

	Acceptable	Acceptable with conditions	No conclusion	total
mononational	**121 (87%)**	**17 (12%)**	**1 (1%)**	**139**
commercial	9 (90%)	1 (10%)	-	10
non-commercial	112 (87%)	16 (12%)	1 (1%)	129
multinational	**10 (67%)**	**5 (33%)**	**-**	**15**
commercial	6 (75%)	2 (25%)	-	8
non-commercial	4 (57%)	3 (43%)	-	7
Total	**131 (85%)**	**22 (14%)**	**1 (1%)**	**154**
Source: Own calculations based on information from the public CTIS portal (13,14)				

Conditions for initial clinical trial applications that were issued by the MSC often affected the update of specific clinical trial documents such as the clinical trial protocol, the IB or study medication labels. Also, inconsistencies in clinical trial documents were highlighted, which are requested to be corrected. In one case it was pointed out that the correct versioning of the clinical trial protocol needed to be implemented according to article 47 of the CTR. In another condition the sponsor is asked to provide relevant Good Manufacturing Practice (GMP) documents. Furthermore, additional assessments and monitoring measures as well as additional or changed statistical analyses were requested through conditions. In one of the conditions the sponsor is asked to provide a commitment to submit safety information of the

first trial phase before inclusion of patients in the second trial phase. In another condition, information about the analysis of biological samples are demanded, as soon as they are available. It is explicitly mentioned that the sponsors response to the Part I assessment RFI was not sufficient in one of the conditions. The conditions issued with conclusion of Part I assessment should mostly be fulfilled by the sponsor with a substantial modification, only in a few cases a non-substantial modification was sufficient (13).

Figure 5 shows the outcome of the Part I assessment by MSC for mononational trials and by RMS for multinational trials respectively.

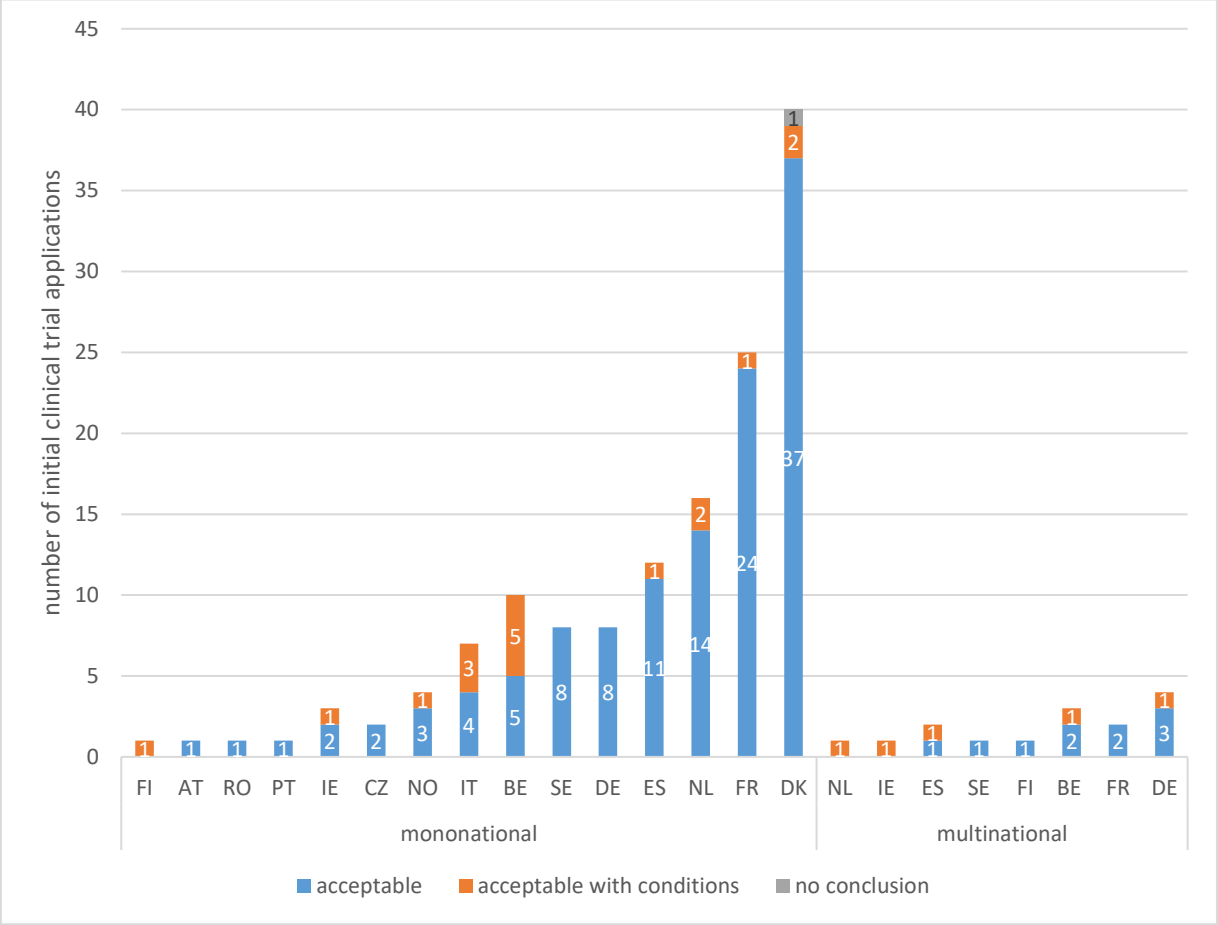

Figure 5: Outcome of Part I assessment by MSC for mononational initial clinical trial applications and by RMS for multinational initial clinical trial applications

Source: Own calculations based on information from the public CTIS portal (13,14)

As already outlined in Table 3, Part I of most of the initial clinical trial applications was fully accepted by each MSC for mononational trials and RMS for multinational trials, respectively. Within mononational initial clinical trial applications Belgium and Italy authorized initial clinical trial applications with conditions only most frequently (n=5; n=3). For multinational trials RMS Germany fully approved Part I of the initial clinical trial application most frequently (n=3) (13).

The outcome of a Part I assessment for one mononational trial in Denmark was listed with “no conclusion” (2022-503010-23-01). This suggest that a tacit approval applied, since the overall status of the trial is authorized. However, the conclusion for Part II assessment was also displayed with “no conclusion” and therefore it is foreseen that the overall trial status will be “under evaluation” (19). No reason for this could be found, although there was one Part I assessment RFI published, no assessment report was available (13).

For one multinational trial (2022-500014-26-00) the initial clinical trial application was withdrawn in Portugal and re-submitted as an addition of a new MSC 6 days after Part I initial trial decision (13). No reason for the withdrawal could be identified since no Part I assessment report or Part I assessment RFI was available in the public CTIS portal (18).

For most of the trials at least one Part I Assessment RFI was published (84%). A Part I assessment RFI was issued slightly more often for initial clinical trial applications for multinational trials (87%) in comparison to initial clinical trial applications for mononational trials (83%). Average number of Part I assessment RFIs for initial clinical trial applications with at least one Part I assessment RFI issued accounts to 1.33 (13).

The maximum number of Part I Assessment RFIs were 6, issued by France for a mononational trial application (2022-502426-41-00) (13). Only the first Part I assessment RFI is covering content related questions, the other Part I assessment RFIs are concerning the functionality of updates of documents within CTIS (20).

No Part I disagreements of MSC with the respective RMS decision were identified. However, it was highlighted by Belgium as MSC for one trial (2022-502049-91-00), that the intention to refuse had not been registered before the RMS had completed the Part I assessment positively. Therefore, the disagreement was highlighted within Part II assessment. The reason

for the disagreement is that the Belgium health authority is questioning the mechanism of action for specific liposomes. In the view of the Belgium health authority, the safety of the patients cannot be guaranteed and therefore the authorization of the initial clinical trial application was refused (13,21).

In total 6 (4%) initial clinical trial applications were listed with previous scientific advice within the public CTIS portal. Only one of them was concerning a mononational trial, the others multinational trials. For the multinational initial clinical trial applications, less applications with a previous scientific advice were fully accepted with 50% compared to 86% without a previous scientific advice. The proportion of initial clinical trial applications which are accepted with conditions only is higher for trials with a previous scientific advice (50% vs. 13%) (13).

4.2.2. Timelines for Part I assessment

After the presentation of the outcome of Part I assessment, the timelines for Part I assessment are presented in the following. Timelines for Part I assessment were calculated from the date of validation conclusion to the date of Part I assessment conclusion from the MSC for mononational initial clinical trial applications and from the RMS for multinational initial clinical trial applications, respectively.

The analyses showed that it took 64 days on average from the validation conclusion date to the Part I assessment conclusion date. The average assessment time for mononational initial clinical trial applications was shorter than for multinational initial clinical trial applications, with 63 days for mononational trials compared to 75 days for multinational trials. There was no significant difference between commercial and non-commercial trials, as shown in Table 4 below.

Table 4: Duration from validation conclusion to Part I assessment conclusion of initial clinical trial applications

	Average in days	Minimum in days	Maximum in days
mononational	**63**	**1**	**101**
commercial	60	30	84
non-commercial	63	1	101
multinational	**75**	**11**	**84**
commercial	82	80	84
non-commercial	66	11	84
Total	**64**	**1**	**101**
Source: Own calculations based on information from the public CTIS portal (13,14)			

The maximum duration for Part I assessment was 101 days, which was observed for one initial clinical trial application for a non-commercial mononational trial with MSC Italy (2022-502907-31-00). One Part I assessment RFI was published for this procedure. The minimum duration was only one day for initial clinical trial application for another non-commercial mononational trial conducted in Denmark (2022-501035-16-01). No Part I assessment RFI was raised for this procedure as well (13).

Figure 6 below is outlining the duration from validation date to Part I assessment conclusion date by MSC for initial clinical trials applications depending to whether a Part I Assessment RFI was received or not. For multinational initial clinical trial applications the Part I assessment conclusion date by RMS is displayed.

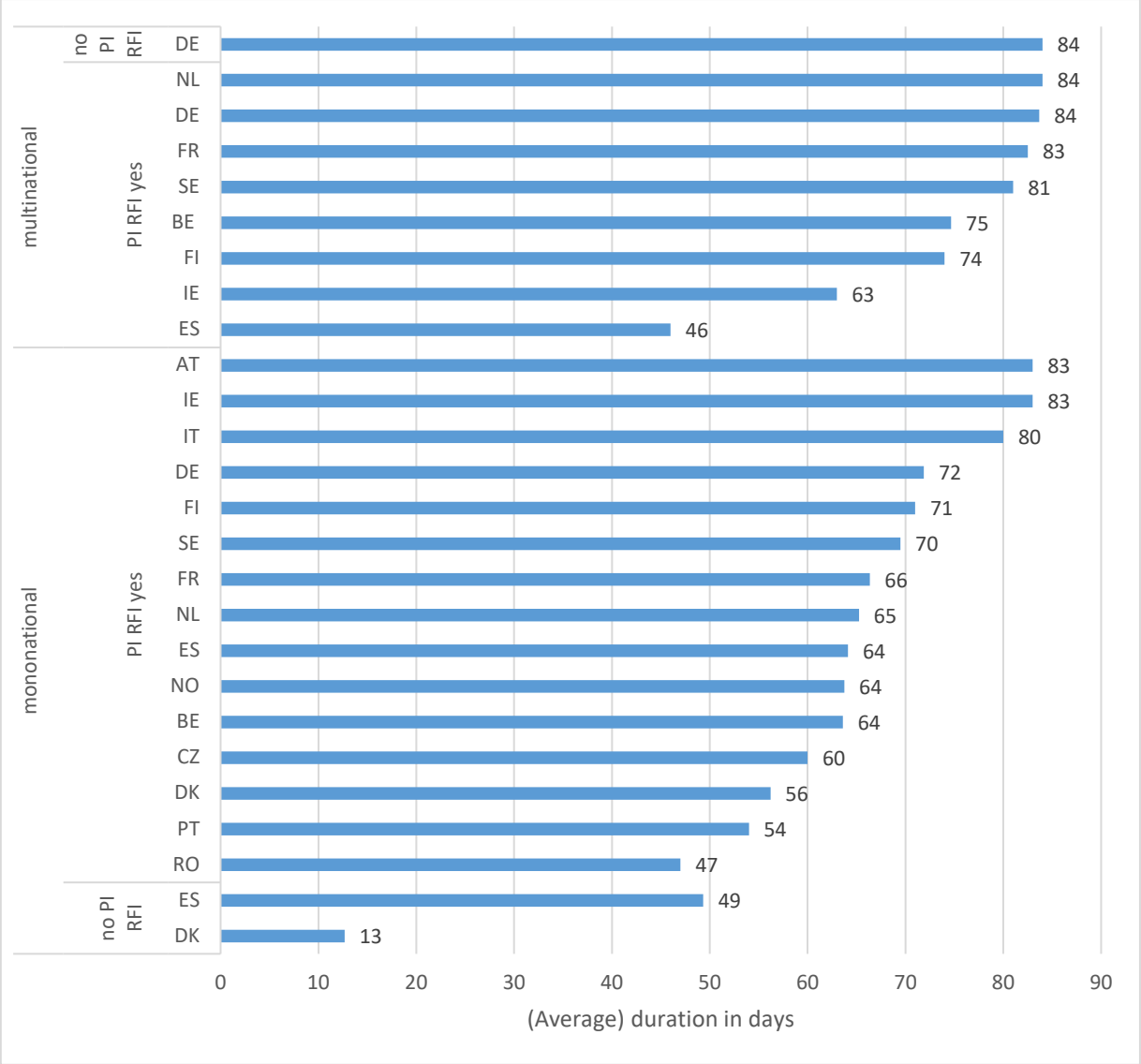

Figure 6: (Average) duration from validation to Part I assessment conclusion by MSC (RMS for multinational trials)

Source: Own calculations based on information from the public CTIS portal (13,14)

For mononational initial clinical trial applications without any Part I assessment RFI, the average duration was ranging from 13 days in Denmark (n=3) to 49 days in Spain (n=3). It has to be noted that one of the 3 mononational trials in Denmark was listed with the Part I assessment conclusion on the next day after the validation conclusion date (2022-501035-16-01). For mononational initial clinical trial applications for which a Part I assessment RFI was

issued, the duration from validation until Part I assessment conclusion ranged from 47 days for Romania (n=1) to 83 days in Austria (n=1) and Ireland (n=3) (13).

Only one multinational initial clinical trial application without any Part I assessment RFI was identified with RMS Germany (2022-500014-26-00). It is unclear, whether a Part I assessment-RFI was actually not issued or not published in CTIS, since no Part I assessment report was published either (18). For multinational initial clinical trial applications for which a Part I assessment RFI was issued the duration ranged between 46 days for RMS Spain (n=1) to 84 days for RMS Germany (n=3) and Netherlands (n=1) (13).

4.3. Part II assessment of the initial clinical trial application

4.3.1. Outcome of Part II assessment

Part II assessment took place in parallel to Part I assessment for all initial clinical trial applications included in the analysis, since no partial initial clinical trial application was identified (13).

For Part II assessment 76% of the initial clinical trial applications received full acceptance by the individual MSCs as outlined in Table 5. A higher percentage of mononational trials were fully accepted by the MSCs than multinational trials, with 88% and 55% respectively (13). Part II of the initial clinical trial application was still listed as “under evaluation” for 19 MSC in the analysis. For 8 MSCs the Part II assessment was listed with “no conclusion”, thus the MSC did not complete the task in time (19).

In total 21 (10%) of the initial clinical trial applications were only approved with conditions by the individual MSC. These conditions concern for example changes within the ICF in order to reflect information to the patient correctly, like contraception, insurance information or mentioning potential negative effects of the treatment on the patient. Moreover, rejection of a direct to patient shipment and conditions for the conduct of a digital patient media campaign were listed. Also, required investigator registrations within CTIS or addition of trial sites were

part of conditions. One condition was also concerning the upload of documents as a response to one of the RFIs. Lastly, the conduct of additional statistical analyses was requested within one of the conditions. The fulfillment of the conditions was requested via a substantial modification explicitly in a few cases (13).

Table 5: Outcome of Part II assessment for initial clinical trial applications

	Acceptable	Accept. w. conditions	No concl.	Not accept.	Under eval.	With-drawn	total
mononational	**123 (88%)**	**14 (10%)**	**2 (1%)**	-	-	-	**139**
commercial	10 (100%)	-	-	-	-	-	10
non-commercial	113 (88%)	14 (11%)	2 (2%)	-	-	-	129
multinational	**42 (55%)**	**7 (9%)**	**6 (8%)**	**2 (3%)**	**19 (25%)**	**1 (1%)**	**77**
commercial	32 (71%)	-	6 (13%)	2 (4%)	4 (9%)	1 (2%)	45
non-commercial	10 (31%)	7 (22%)	-	-	15 (47%)	-	32
Total	**165 (76%)**	**21 (10%)**	**8 (4%)**	**2 (1%)**	**19 (9%)**	**1 (1%)**	**216**

Accept. = Acceptable; concl. = conclusion; eval. = evaluation; w. = with.
Source: Own calculations based on information from the public CTIS portal (13,14)

Part II of the initial clinical trial application was considered as not acceptable by Belgium for two multinational trials (2022-502049-91-00 & 2022-500014-26-00). One of these rejections was meant to be a disagreement with Part I assessment, as already outlined in chapter 4.2.1 above (2022-502049-91-00). For the other initial clinical trial application (2022-500014-26-00), no information was provided for the non-acceptance and no Part II assessment report was available in the public CTIS portal (13).

Furthermore, one Part II initial clinical trial application was withdrawn in Austria for a multinational trial (2022-502049-91-00) (13). The entry for Austria was empty in the public CTIS portal, therefore no further information on the withdrawal could be retrieved (21).

For most of the Part II assessments at least one Part II assessment RFI was published by the individual MSC (87%). A Part II assessment RFI was issued for a higher proportion of initial clinical trial applications for mononational trials (94%) in comparison to initial clinical trial applications for multinational trials (76%). Average number of Part II assessment RFIs for initial clinical trial applications for which at least one Part II assessment RFI was issued accounts to 1.40 (13).

The maximum number of issued Part II Assessment RFIs are 5 from the Danish health authority for a mononational trial (2022-500906-17-01). These 5 Part II assessment RFIs were mostly issued after sponsor response to each of the previous RFIs, referring to the sponsors feedback and actions taken by the sponsor, like the update of informed consent forms (22).

4.3.2. Timelines for Part II assessment

The consideration of the timelines for Part II assessment showed that it took 68 days on average from validation conclusion date to Part II assessment conclusion date. The decision time for mononational initial clinical trial applications was shorter than for multinational initial clinical trial applications with 57 days versus 93 days on average, as outlined in Table 6 (13).

The maximum duration for Part II assessment of a mononational initial clinical trial application counted to 158 days for a trial conducted in Denmark (2022-502500-75-00). For multinational initial clinical trial applications, the maximum was 210 days, which was observed for the Part II assessment from Spain and Poland of one trial (2022-500449-26-00).

There was a difference between commercial and non-commercial trials noticed for multinational trials for the average duration from validation conclusion to Part II assessment conclusion. Commercial trials received Part II assessment conclusion in average 18 days faster than non-commercial trials.

Table 6: Duration from validation conclusion to Part II assessment conclusion of initial clinical trial applications

	Average in days	Minimum in days	Maximum in days
mononational	**57**	**9**	**158**
commercial	51	28	77
non-commercial	58	9	158
multinational	**93**	**13**	**210**
commercial	88	37	192
non-commercial	106	13	210
Total	**68**	**9**	**210**
Source: Own calculations based on information from the public CTIS portal (13,14)			

Next, the duration from validation date to Part II assessment conclusion date for initial clinical trial applications depending to whether a Part II Assessment RFI was received or not is illustrated for mononational trials in Figure 7 and multinational trials in Figure 8 below.

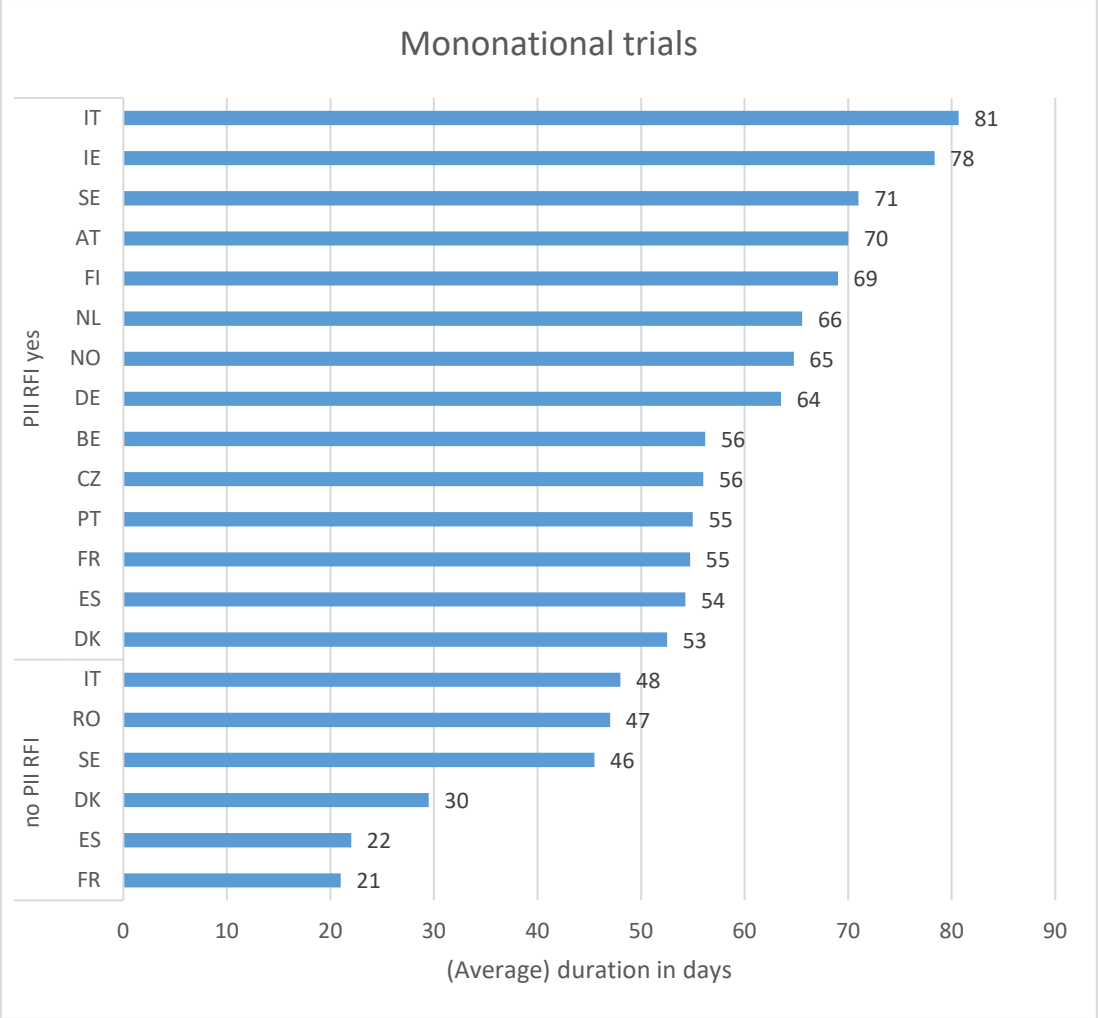

Figure 7: (Average) duration from validation to Part II assessment conclusion by MSC for mononational initial clinical trial applications

Source: Own calculations based on information from the public CTIS portal (13,14)

There was a significant difference in the duration for assessment of Part II assessment between the different MSC, ranging from 21 days on average in France (n=2) up to 81 days for Part II assessment on average in Italy (n=7). Part II assessment for mononational initial clinical trial applications for which no Part II assessment RFI was published in the public CTIS portal was significantly shorter than for applications for which a Part II assessment RFI was issued, with an average of 34 days without a Part II assessment RFI compared to 59 days with Part II assessment RFI (13).

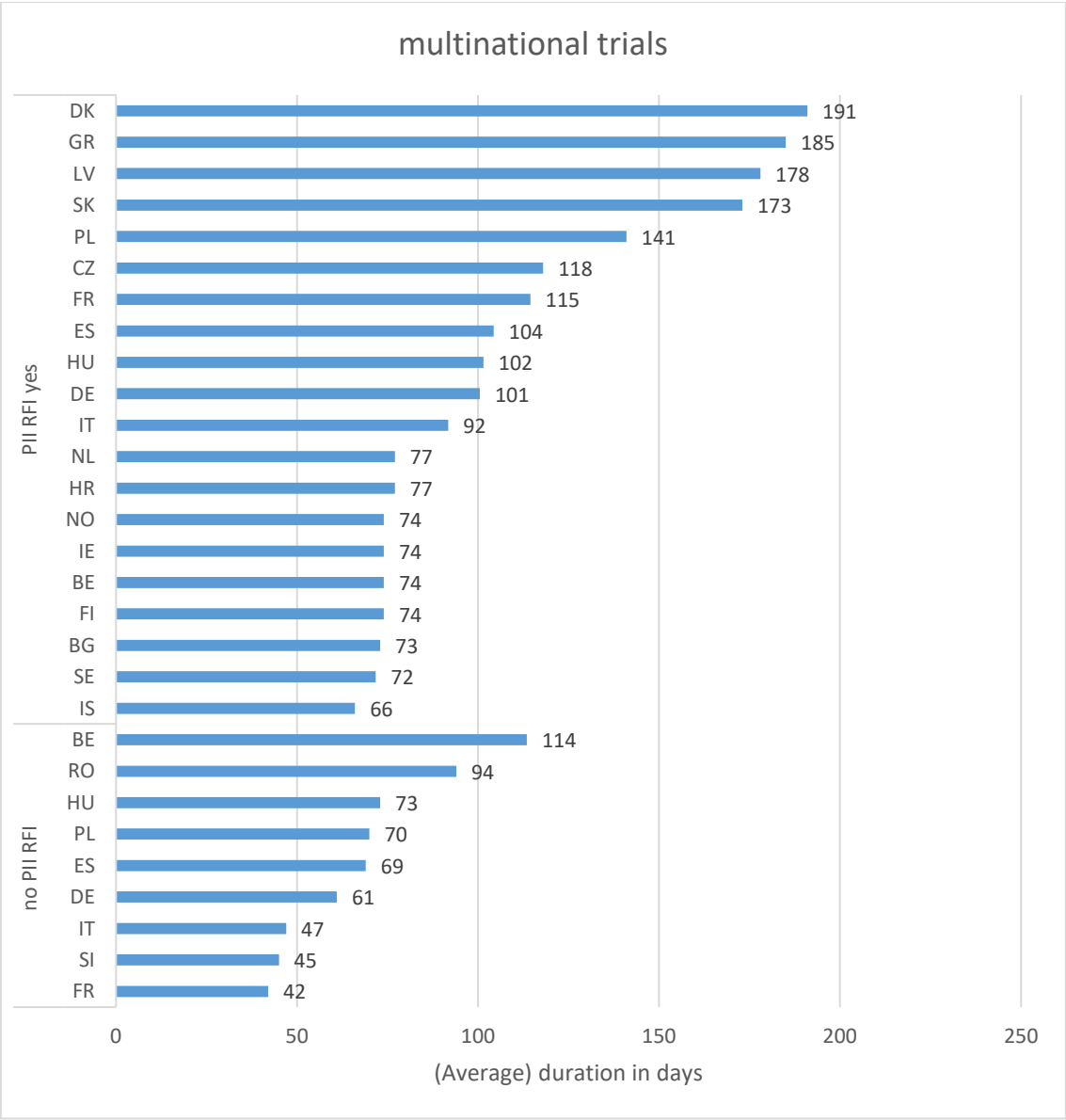

Figure 8: (Average) duration from validation to Part II assessment conclusion by MSC for multinational initial clinical trial applications

Source: Own calculations based on information from the public CTIS portal (13,14)

For initial clinical trial applications for multinational trials there was also a wide range of the average duration of the Part II assessment, starting with 42 days in average for a trial conducted in Italy with no previously issued Part II assessment RFI (n=4) and counting up to 191 days for MSC Denmark with a previously raised Part II assessment RFI (n=1).

4.4. Decision of each MSC about the initial clinical trial application

4.4.1. Duration from Part I or Part II conclusion to decision

Last step in the authorization process of an initial clinical trial application under the CTR is the decision by each MSC, which needs to be noticed to the sponsor within 5 days after the Part I or Part II assessment conclusion date (11). For the following analysis of the duration from Part I or Part II assessment conclusion to decision by each MSC, the decision date was taken from the overall trial status table on the summary tab in the public CTIS portal. The duration until decision was either calculated using Part I assessment conclusion date or Part II assessment conclusion date, depending on which date was later.

Some inconsistencies in the information about the decision date in the public CTIS portal were identified. There was one initial clinical trial application where the Part II assessment conclusion date from the MSC Italy was in December 2022, the Part I assessment conclusion date in February 2023 and the decision date not before May 2023 (2022-501822-39-00). Moreover, there were decision dates for 3 different MSC which were each before the Part II assessment conclusion date (2022-502267-37-00 for Hungary and Poland; 2022-500587-35-01 for Sweden). The decision date in all three cases was corresponding to the submission date of the initial clinical trial application. Due to these inconsistencies, these initial clinical trial applications were excluded from the analysis of the decision timelines.

Additionally, there were some cases with a decision date listed for the individual MS, despite the Part II assessment conclusion is still “under evaluation” (2023-503244-14-00; 2022-500587-35-01; 2022-501132-42-00). Since the authorization status for Part I was “acceptable” or “acceptable with conditions”, these could not have been tacit approvals (19). Thus, since no plausible reason for this deviation could be found, these were excluded from the analysis of the decision timelines.

Table 7: Duration from Part I or Part II assessment conclusion to decision by MSC for initial clinical trial applications

	Average in days	Minimum in days	Maximum in days
mononational	**1**	**0**	**7**
commercial	1	0	4
non-commercial	1	0	7
multinational	**4**	**0**	**24**
commercial	5	0	24
non-commercial	3	0	7
Total	**2**	**0**	**24**
Source: Own calculations based on information from the public CTIS portal (13,14)			

As displayed in Table 7, the average duration from Part I or Part II assessment conclusion date, whichever is later, to MSC decision date was 2 days, with an average of 1 day for mononational trials and 4 days for multinational trials. Minimum duration was zero days, meaning the decision date was on the same date as the Part I or Part II conclusion date and. Maximum duration for decision from Part I or Part II conclusion date summed up to 24 days.

Figure 9 illustrates the duration from Part I or Part II assessment conclusion date to decision date for initial clinical trial applications by MSC.

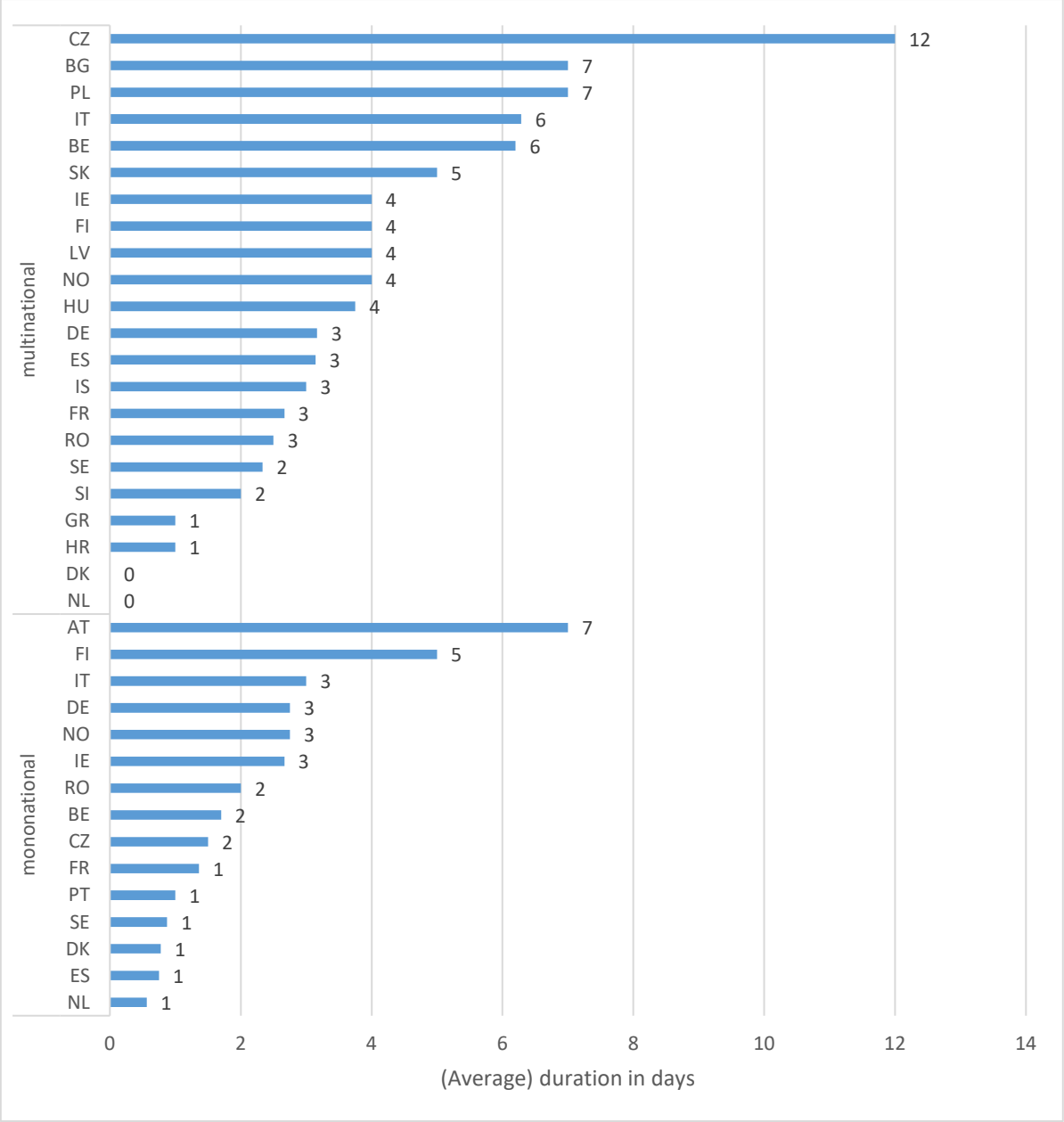

Figure 9: (Average) duration from Part I or Part II assessment conclusion to decision by MSC

Source: Own calculations based on information from the public CTIS portal (13,14)

Two multinational trial applications with decision date on the same date as Part II assessment conclusion were listed for Denmark and Netherlands (2022-500449-26-00; 2022-501811-14-00) (13).

The average duration of 12 days for the Czech Republic to notify the decision to the RMS resulted from two multinational initial clinical trial application, one with 2 days between Part I assessment conclusion and decision date (2022-502921-16-00) and one with 22 days between Part II assessment conclusion and decision date (2022-502049-91-00) (13).

4.4.2. Duration from submission to decision

Lastly, the overall time from submission of the initial clinical trial application to decision of each MSC is displayed.

The average duration from initial clinical trial submission date to decision date was 98 days, as outlined in Table 8. The average duration was shorter for mononational initial clinical trial applications with 83 days compared to 133 days for multinational initial clinical trial applications. No big difference between commercial and non-commercial trials was be noticed within mononational or multinational initial clinical trial applications (13).

The maximum duration of 245 days occurred for one non-commercial multinational trial for MSC Poland (2022-500449-26-00) (13).

Table 8: Duration from submission to decision by MSC for initial clinical trial applications

	Average in days	Minimum in days	Maximum in days
mononational	**83**	**26**	**181**
commercial	73	35	111
non-commercial	84	26	181
multinational	**133**	**0**	**245**
commercial	133	0	223
non-commercial	133	0	245
Total	**98**	**0**	**245**
Source: Own calculations based on information from the public CTIS portal (13,14)			

Figure 10 displays the total duration from submission of the initial clinical trial application to decision date by MSC.

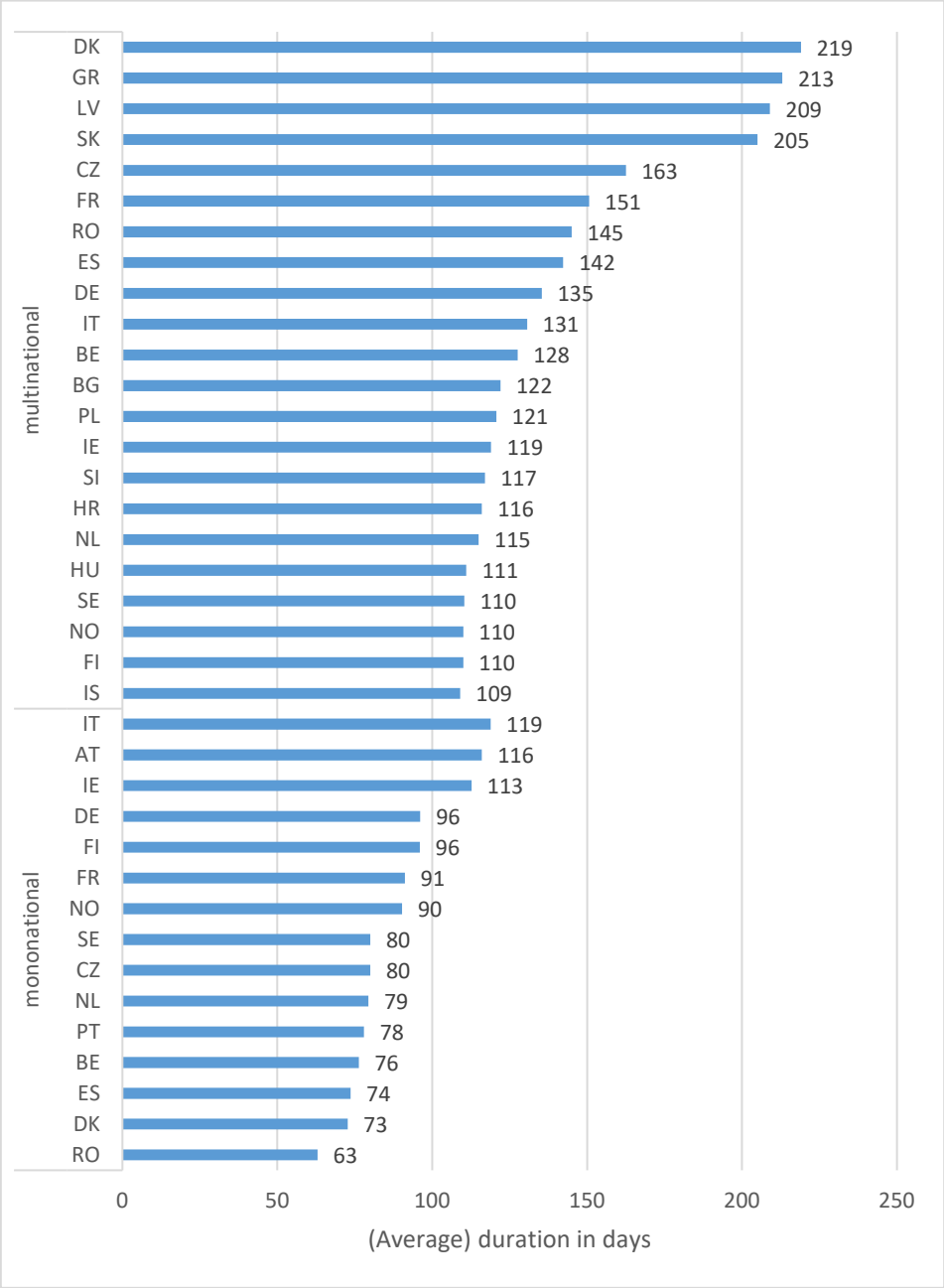

Figure 10: (Average) duration from submission of the initial clinical trial application to decision by MSC

Source: Own calculations based on information from the public CTIS portal (13,14)

A wide range was noticed for the duration from initial clinical trial application submission date to decision by MSC, for both, mononational and multinational initial clinical trial applications.

For multinational trials the duration from submission to decision ranged from 109 days in Iceland (n=1) up to 219 days in Denmark (n=1). For mononational trial applications a comparable range was shown with 63 days in Romania (n=1) up to 119 days in Italy (n=7) (13).

5. Discussion

Limitations of the analysis

Given the results previously presented, relevant limitations are discussed in the following. Main limitation is the data basis of only 154 initial clinical trial applications in the analysis compared to 761 trials with a decision under the CTR as of June 2023 (10). This limits the significance of the results, since only 28% of all initial clinical trial applications with a decision under the CTR are included. Moreover, the proportion of initial clinical trial applications for mononational and multinational trials as well as commercial and non-commercial trials is differing from the numbers reported by the EMA as of end of June 2023 as shown in Table 9.

Table 9: Initial clinical trial applications with a decision in CTIS according to EMA in comparison to initial clinical trial applications included in the analysis

	EMA reported numbers as of end of June 2023 (10)	**Included within the analysis as of July 2023** (13)
mononational	**412**	**139**
commercial	195	10
non-commercial	217	129
multinational	**349**	**15**
commercial	318	5
non-commercial	31	5
Total	**761**	**154**
EMA = European Medicines Agency.		

Thereby, mononational, non-commercial trials are overrepresented in the analysis which leads to a bias of the results. Moreover, 26% of all identified initial clinical trial applications are mononational trials which are conducted in Denmark by non-commercial sponsors (n=40), leading to an additional bias of the results. The high number of initial clinical trial applications for mononational, non-commercial trials in Denmark identified in this analysis is surprising. It does not correspond to the figures which are reported by the EMA, where the most clinical trials with a decision are listed for Spain, France, Germany and Italy (10).

Interestingly, the number of initial clinical trial applications listed in the public CTIS portal remained the same from data cut-off end of July 2023 until submission of this master thesis mid of September 2023.

Since only 10% (n=15) of all included initial clinical trial applications in the analysis concern multinational trials, the analyses for multinational trials are subject to a further limitation. The proportion is significantly lower than reported by the EMA. By the end of June 46% of all initial clinical trial applications with a decision in CTIS were concerning multinational trials (10).

Additionally, there is a potential bias due to the voluntary use of the CTR process until 31st January 2023, as well as possible limited data reliability due to system and user difficulties at the beginning of the implementation. Some technical difficulties were also encountered during the performance of the analysis, such as downloading or viewing of Part I assessment reports. For some of them, this was technically not possible although the pdf appeared to be available on the website. Also, some of the assessment reports were missing completely. Information such as the RMS for multinational trial was not directly available in a few cases and needed to be concluded from the information within the validation RFI.

Lastly, although numerous quality checks were carried out for the analysis, errors cannot be entirely ruled out, particularly in the details of the manual extraction of the additional information from the public CTIS portal.

Despite these limitations, the results of this analysis are still rated as valuable, as they provide new evidence about the current status of initial clinical trial applications within the public CTIS portal as of the end of July 2023.

Some interesting and surprising findings were revealed about the outcomes and timelines of initial clinical trial applications, which are displayed in Table 10.

Table 10: Key findings of the analysis

General:

- Limited availability of published trials within the public CTIS portal.
- Impact of technical issues of CTIS reflected in public portal.

Outcome:

- Unknown reasons for non-authorization of applications.
- No invalidation of any initial clinical trial application.
- High maximum number of RFI for validation, Part I and Part II.
- Conditional approvals not compliant with CTR intention.
- No positive impact of preceding scientific advice.

Timelines:

- The maximum duration for validation, Part I and Part II assessment is longer than specified in the CTR.
- The average duration from validation to Part II assessment for multinational trials is longer than specified in the CTR.

These key findings are elaborated further below.

Limited availability of published applications in the public CTIS portal

The limited availability of published trials within the public CTIS portal is due to a technical issue, which is already know by the EMA. Trials with any kind of deferral, and if only applicable for the protocol, are not published within the public CTIS portal since mid-August 2022. The EMA is currently working on solving the issue (10).

According to Art. 81 (4) of the CTR, information within CTIS should be made publicly accessible, unless for specific exceptions, e.g. to protect personal data or commercially confidential information (3). Since only a small proportion (28%) of all initial clinical trial applications with a decision under the CTR is published until now, the transparency goal of the CTR cannot yet be considered as achieved.

Moreover, the initial clinical trial applications which are not available within the public CTIS portal yet suggest that deferrals are mainly used from commercial sponsor for applications concerning multinational studies.

Impact of technical issues of CTIS

Lastly, the analysis revealed that previously reported user difficulties and technical issues are also reflected in the public CTIS portal. Examples are the 6 Part I Assessment RFI issued by France, which are mostly concerning the functionality of updates of documents within CTIS. Additionally, one Part II condition from Belgium was intended as an Opt-Out for Part I assessment, which could not be addressed during Part I assessment due to technical difficulties. Interestithngly, no further information is available, if and how the concerns from the Belgian health authority regarding the patient safety were handled.

As soon as the technical issue with the deferrals is fixed and all trials with a decision are published in the public CTIS portal, an update of this analysis is considered useful to re-evaluate the findings. However, as the process evolves over time, the results may also vary from the current findings of this analysis.

Unknown reasons for non-authorization of applications

For initial clinical trial applications which were not authorized, there are no further information available within the public CTIS portal. The rationale for the non-authorization of these applications is therefore not known.

Considering the transparency approach of the CTR this is viewed critically, since the reason for non-authorization of initial clinical trial applications might be an interesting information, especially to patients and physicians. Moreover, no lapsed, withdrawn or halted initial clinical

trial applications are publicly available in the public CTIS portal so far, although there are some applications with such a decision in CTIS according to EMA (10).

The Clinical Trials Coordination and Advisory Group (CTAG) explicitly mentions the publication of information on refused trials on the public CTIS portal, *"in order to promote trust in the society"* (7). Based on the results of this analysis, this intention of the CTR is considered as not yet achieved. However, this might also be due to a technical issue and it remains to be seen what information will be visible in the public CTIS portal once all technical problems are solved.

No invalidation of any initial clinical trial applications

Surprisingly, none of the initial clinical trial application included within the analysis was invalidated during the validation phase. This indicates either a high quality of applications, or the invalidated applications were not published. The EMA reports that 87 clinical trial applications are lapsed so far; however, this could have also been for other reasons such as missing sponsor response to Part I assessment (7,10).

High number of RFIs for validation, Part I and Part II assessment

It is also surprising that the maximum number of published RFIs is remarkably high, reaching up to 4, 6 and 5 for validation, Part I and Part II assessment respectively. It was anticipated that only a single RFI would be raised during the assessment phase (9). Nevertheless, this analysis reveals that more than one RFI is frequently raised during validation, Part I and Part II assessment. Some of the RFIs cite insufficient sponsor response or technical complications with the upload in CTIS as the reasons for this. The upcoming procedures will show whether this is due to the initial difficulties with use of CTIS, or whether this will become common practice.

Conditional approvals not compliant with CTR intention

The evaluation of the conditions, which were raised along with the approvals with conditions for Part I or Part II assessment, reveals, that many of the conditions are not compliant with the requirements of the CTR. As laid out in Art. 8 (1) of the CTR, conditions should only be raised in case the condition cannot be fulfilled by the time of authorization (3). The Part I and Part II

conditions identified within this analysis are often concerning updates of the protocol or other trial documents and do not seem to fulfill this requirement.

Part I and Part II conditions are often very specific for the individual trial. Nevertheless, some general insights for further initial clinical trial applications can be gained, which might be helpful for future initial clinical trial applications:

- DMC charter must be included for Data Monitoring Committees including names and qualifications of each member.
- The trial title has to reflect inclusion criteria correctly.
- New versions of study protocols must be provided with new version numbers as well as release date.

No positive impact of preceding Scientific Advice

The analysis also revealed an unexpected finding that obtaining previous scientific advice does not have a positive influence on the Part I assessment outcome. The assumption was that obtaining previous scientific advice would result in a favorable outcome for the Part I assessment. However, initial clinical trial applications with previous scientific advice were more accepted with conditions only compared to initial clinical trial applications without a previous scientific. However, since the conditions were often formalistic, it seems they were not related to the previous scientific advice.

The maximum duration for all authorization process steps is longer than specified in the CTR.

Although the average duration for validation, Part I, Part II assessment or decision by each MSC is in line with the specified timelines of the CTR, in several instances, the maximum duration is longer than stated. This is unexpected since timelines are set for each phase and recorded accordingly in CTIS.

One possible reason for maximum durations only slightly higher than specified is that due dates must fall on a working day and can slightly prolong the maximum duration, which were not considered in the calculations. Also, national public holidays for the individual MSC were

not taken into account. However, it is still surprising that the maximum duration deviates with up to 134 days from the CTR specifications, as shown in Table 11.

Table 11: Maximum duration for initial clinical trial authorization procedure steps observed in the analysis compared to CTR specifications

	Maximum duration in days observed in the analysis (13)	Maximum duration in days as specified by the CTR (3,7)
Validation		
Mononational	42	25
Multinational	32	
Part I assessment		
Mononational	101	76*
Multinational	84	
Part II assessment		
Mononational	158	76
Multinational	210	
Decision		
Mononational	7	5
Multinational	24	

* Extension up to 50 additional days according to article 18 (5) of the CTR in case consultation of experts is needed is not taken into account for standard maximum timelines

CTR = Clinical trial regulation.

As per article 8 (6) of the CTR it is intended that the timelines in CTIS are adhered to and otherwise automatic decisions like lapse of the application or tacit decision are automatically performed (3). It is therefore questionable whether the calculation of timelines in CTIS is always correct or if this could also play a role. The timeline for Part I assessment can be extended up to 50 days if experts are involved. However, no information could be found on such an involvement and it is questionable whether this is so often relevant.

In conclusion, the duration from submission of the initial clinical trial application to the final notification of the decision to the sponsor took longer than foreseen from the CTR quite frequently. According to the EMA, the average duration from submission to decision is 90 days (10), which corresponds with the average duration of 98 days from submission to decision in this analysis.

The average duration from validation to Part II assessment for multinational trials is longer than specified in the CTR.

In addition to the duration of all authorization process steps exceeding the specified maximum in the CTR, the average duration from validation to Part II assessment conclusion is also longer than the specified duration for multinational clinical trial applications. For individual MSCs, the average time taken for Part II assessment in multinational trials was 93 days, instead of 76 days as foreseen by the CTR (3,7). As a result, the overall duration from submission to decision was also longer than expected for initial clinical trial applications concerning multinational trials, with 133 days in average compared to 106 days as specified in the CTR (3,7). There is no clear explanation for this discrepancy since timelines are assumed to be set for each phase in CTIS without any deviations.

6. Conclusion/Outlook

A comprehensive picture and unexpected new insights about the initial clinical trial applications, which are published in the public CTIS by the end of July 2023, are revealed by this analysis. All pre-defined objectives about the outcomes and timelines of the first initial clinical trial applications which were submitted under the legal framework of the CTR could be answered.

Due to the limited availability of published trials in the public CTIS portal, initial clinical trial applications for mononational non-commercial trials are overrepresented within this analysis. Especially initial clinical trial applications in Denmark make up a significant proportion of all trials included in the analysis. Despite the limitations, the overall results of this analysis on the

outcome of initial clinical trial applications and the average duration for validation, Part I and Part II assessment and final decision are comparable to the figures which are reported by the EMA for all initial clinical trial applications in CTIS as of end of June 2023.

One of the insights generated through this analysis is that the reason for non-authorization of initial clinical trial applications is missing from the public CTIS. Since the reasons for non-authorization of initial clinical trial applications might provide interesting information for the public, the intent of the CTR for greater transparency through more publicly available information can therefore not be seen as fully accomplished yet.

The maximum number of published RFIs during the assessment of clinical trial applications is surprisingly high, with multiple RFIs being frequently raised during validation, Part I and Part II assessment, instead of just one as anticipated.

Further observations were made regarding non-compliance with CTR specifications concerning the conditions for approvals with conditions. Most of the conditions which were issued for Part I or Part II assessments do not meet the requirement of the CTR, that they could not have been fulfilled by the time of authorization.

In terms of timelines, the maximum duration of all process steps during the authorization of an initial clinical trial application is not in line with the maximum timelines set by the CTR. The maximum duration for validation, Part I and Part II assessment and final decision exceeded the stipulated timeframe in the CTR up to 104 days. Subsequently, also the maximum duration from submission of the initial clinical trial application to decision by each MSC was up to 139 days longer than specified in the CTR.

Moreover, the average duration from validation to Part II assessment conclusion for multinational trials exceeds the specified maximum timelines set by the CTR by 17 days. Consequently, the average duration from submission to decision was 27 days longer than expected for initial clinical trial applications concerning multinational trials. The identified deviations from the deadlines are surprising because the expectation was that CTIS adheres to strict rules for evaluation timelines and allows no deviations from the harmonized process.

Lastly, technical problems encountered with CTIS which have been reported by different stakeholders before are also evident in the public CTIS portal. Examples are inconsistencies in decision dates, RFI requests which were necessary for technical document updates, and a specific Part I disagreement that needed to be addressed during Part II assessment.

All in all, this analysis reveals new and surprising information about the first initial clinical trial applications which were submitted in CTIS within 1.5 years after its implementation. Further observation of the information in the public CTIS portal allows to track changes over time. As the process continues to evolve, certain findings may also change during the course of time. Nevertheless, an idea for the future is to maintain the database through regular updates, maybe even with the use of an Artificial Intelligence (AI). Given the digital era we live in, an AI might open up new possibilities to perform upcoming updates of the analysis.

7. Summary

In January 2022 the CTR, the Regulation (EU) No 536/2014, became applicable within the EU, replacing the former legal basis CTD (Directive 2001/20/EC). Along with the CTR major changes in the regulatory environment for clinical trials in the EU were introduced. Prerequisite for the CTR to become applicable within the EU was the functionality of CTIS, a single-entry point for clinical trial applications in. All information about clinical trials as well as all communication between stakeholder is performed via CTIS for initial clinical trial applications under the legal framework of the CTR.

One part of CTIS is a public CTIS portal, which is intended to offer more transparency about clinical trials within the EU to the public. Basis for this master thesis were all initial clinical trial applications within the public CTIS portal by the end of July 2023. All published initial clinical trial applications by this time have been systematically analyzed. This was done via extraction of relevant information from the public CTIS portal and subsequent compilation in a database. Based on the information in the database, analyses and calculations were performed to answer the research questions.

One of the insights generated through this analysis is that the reason for non-authorization of initial clinical trial applications is missing from the public CTIS, which limits the transparency of the process. Moreover, non-compliance with CTR specifications concerning approvals with conditions was identified. Some of the conditions which were issued by the MSC to not meet the requirement of the CTR that they could have been fulfilled by the time of authorization.

The maximum number of published RFIs during the assessment of clinical trial applications observed in the analysis were surprisingly high, with multiple RFIs being frequently raised during validation, Part I and Part II assessment, instead of just one as anticipated.

In terms of timelines, the maximum duration of all process steps during the authorization of an initial clinical trial application is not in line with the maximum timelines set by the CTR. The maximum duration for validation, Part I and Part II assessment and final decision exceeded the stipulated timeframe in the CTR. Subsequently, also the maximum duration from submission of the initial clinical trial application to decision by each MSC was longer than specified in the CTR.

Moreover, the average duration from validation to Part II assessment conclusion for multinational trials exceeds the specified maximum timelines set by the CTR. Consequently, the average duration from submission to decision was longer than expected for initial clinical trial applications concerning multinational trials. The identified deviations from the deadlines are surprising because the expectation was that CTIS adheres to strict rules for evaluation timelines and allows no deviations from the harmonized process.

Lastly, technical problems encountered with CTIS which have also been reported by different stakeholders before are also present in the public CTIS portal. Examples for these technical issues are inconsistencies in decision dates, RFI requests which were necessary for technical document updates, and a specific Part I disagreement that needed to be addressed during Part II assessment.

Due to the limited availability of published trials in the public CTIS portal, initial clinical trial applications for mononational non-commercial trials are overrepresented within this analysis. Especially initial clinical trial applications in Denmark make up a significant proportion of all

trials included in the analysis. However, the overall results of this analysis on the outcome of initial clinical trial applications and the average duration for validation, Part I and Part II assessment and final decision are comparable to the figures which are reported by the EMA for all initial clinical trial applications in CTIS as of end of June 2023.

Despite the limitations, new evidence about the first initial clinical trial applications under the legal framework of the CTR was gained with this analysis. The systematic approach revealed interesting and partly surprising results about the outcomes and timelines of initial clinical trial applications published in the public CTIS portal as of end of July 2023. An idea for the future is to maintain the database through regular updates to trace changes over time, as the implementation of initial clinical trial applications under the CTR evolves.

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9. Appendix

Appendix 1: Parameters extracted from the public CTIS portal via automatic download function

Title of the clinical trial
Trial number
Overall trial status
Countries where the trial is taking
Overall start/end date of the trial
Decision date
Conditions
Therapeutic area
Recruitment status
Sponsor/Co-Sponsors
Sponsor type
Trial phase
End point
Product
Age group
Gender
Trial region
Total number enrolled
Overall end of the trial
Primary end point
Results first received
Last updated

Appendix 2: Parameters extracted from the public CTIS portal via manual extraction

Summary – trial information: first submitted (dd.mm.yyyy)
Summary – transition trial yes/no
Full trial information: Trial details - Scientific advice (yes/no)
Events – Serious breach / unexpected event / urgent safety measure / Inspection report from country outside EAA / Temporary halt (yes/no)
Corrective measures (yes/no)
Inspection records (yes/no)
Initial application – submission and decision date (dd.mm.yyyy)
Part I – Validation – submission date (dd.mm.yyyy)
Part I – Validation-RFI published (yes/no), number of RFI
Part I - Validation conclusion
Part I - Validation date (dd.mm.yyyy)
Part I - Assessment conclusion
Part I - Assessment Conclusion date (dd.mm.yyyy)
Part I - AR published (yes/no)
Part I - Assessment-RFI published (yes/no), number of RFI
Part I – RMS
Part I - Disagreements published (yes/no)
Part II - Assessment conclusion
Part II - Assessment Conclusion date (dd.mm.yyyy)
Part II Assessment-RFI published (yes/no), number of RFI
Applications – Substantial modifications (yes/no), if yes number of substantial modifications
Applications – Non-Substantial modifications (yes/no), if yes number of non-substantial modifications
Applications – Addition of new MSC (yes/no), if yes number of addition of new MSC procedures
AR = Assessment Report; EEA= European Economic Area; MSC = Member State Concerned; RFI = Request for Information; RMS = Reporting Member State.

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Nürnberg, 18. September 2023

Unterschrift der Studierenden

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