National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

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(Mis)Match between registration and notification in the Netherlands

RIVM Letter report 2017-0172
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Colophon

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Synopsis

Clinical investigations involving medical devices
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In order to show that medical devices are safe and functional, it is necessary to do research in humans (clinical trials). In order to ensure the safety of the trial subjects (healthy volunteers or patients) and the scientific quality of this type of research, before the trial starts a Medical Ethics Review Committee (MERC) evaluates it to make sure it has been designed properly. This committee also assesses the trial to see if it is acceptable from an ethical point of view. If a clinical trial is carried out on a medical device that does not carry the CE mark, the trial must also be submitted to the Dutch Health and Youth Care Inspectorate in formation (IGJ). This is known as the 'obligation to notify'.

Research carried out by the National Institute for Public Health and the Environment (RIVM) has shown that clinical trials are not always submitted to the IGJ. This could be because applicants are not aware of their obligation to notify, or because the clinical trial is only submitted when the study is actually starting. From 2015-2017, the number of notifications of clinical studies increased when compared with 2011-2013. This may be because the obligation to notify is now better recognised.

In recent years, the IGJ and the Central Committee on Research Involving Human Subjects (CCMO) have been working together to actively spread information about this legal obligation. Applicants to MERCs for clinical trials reported their sources of information about the obligation to notify as being the websites of the IGJ and the CCMO, part of standard procedures at their hospitals, and training courses for researchers.

Keywords: medical devices; clinical investigation; notification; competent authority; CE-mark

Publiekssamenvatting

Klinisch onderzoek met medische hulpmiddelen
(Mis)match tussen registratie en notificatie in Nederland

Om aan te tonen dat medische hulpmiddelen veilig en functioneel zijn, is onderzoek bij mensen nodig (klinisch onderzoek). Om de veiligheid van de proefpersonen (gezonde vrijwilligers of patiënten) en de wetenschappelijke kwaliteit van dit soort onderzoek te bewaken, beoordeelt een medisch-ethische toetsingscommissie (METC) van tevoren of een studie goed is opgezet. Deze commissie beoordeelt ook of de studie ethisch gezien acceptabel is. Als een klinisch onderzoek wordt uitgevoerd met een niet CE-gemarkeerd medisch hulpmiddel, moet het onderzoek ook aangemeld worden bij de Inspectie Gezondheidszorg en Jeugd in oprichting (IGJ i.o.). Dit staat bekend als de zogeheten notificatieplicht.

Uit onderzoek van het RIVM blijkt dat deze klinische onderzoeken niet altijd worden gemeld bij de IGJ i.o. Dit kan komen doordat aanvragers niet bekend zijn met de notificatieplicht of omdat het klinisch onderzoek pas wordt gemeld als het onderzoek daadwerkelijk van start gaat. In de periode 2015-2017 is het aantal genotificeerde klinische onderzoeken wel toegenomen ten opzichte van 2011-2013. Mogelijk komt dit doordat de notificatieplicht nu beter bekend is.

Afgelopen jaren heeft de IGJ i.o. in samenwerking met de Centrale Commissie Mensgebonden Onderzoek (CCMO) actief informatie over deze wettelijke verplichting verstrekt. Aanvragers van klinisch onderzoek bij de METC's noemden als informatiebron over de notificatieplicht de websites van de IGJ i.o. en de (CCMO), de standaardprocedures van hun ziekenhuis en cursussen voor onderzoekers.

Kernwoorden: medische hulpmiddelen; klinisch onderzoek; notificatie; bevoegde instantie; CE-markering

Contents

Summary

This report describes an evaluation of compliance to the notification obligation of clinical investigations with medical devices. Clinical investigations with medical devices have to be performed according to European Directives, guidelines and standards. At Member State level, European Directives are implemented in national legislation. In the Netherlands, the Health and Youth Care Inspectorate (IGJ) is the national competent authority (NCA) for clinical investigations with medical devices. Furthermore, the Central Committee for Research Involving Human Subjects (CCMO) is the competent authority for investigations involving human subjects. Registration at the CCMO by completion of the General Assessment and Registration form (ABR-form) is mandatory for those clinical investigations falling within the scope of the Medical Research Involving Human Subjects Act.

After registration at the CCMO and positive opinion of the medical ethics committee, but before the start of a study, notification to the IGJ is obligatory for clinical investigations with devices bearing a Conformité Européenne mark (CE mark) for purpose(s) outside the scope of the CE-registration and non-CE-marked medical devices. In the last years, both IGJ and CCMO actively disseminated information on this legal notification obligation to improve the notification rate. In order to examine the impact of this, IGJ commissioned the National Institute for Public Health and the Environment (RIVM) to evaluate the notification rate in the period January 2015- June 2017.

In this evaluation, the RIVM compared data from IGJ and CCMO on clinical investigations with medical devices registered and/or notified in 2015-2017. This comparison revealed mismatches concerning clinical investigations that were registered at the CCMO, but were not notified to the IGJ.

For examining the reasons for non-notification, a CCMO enquiry on the notification of investigations to IGJ was used. This enquiry revealed that the main reason for not notifying an investigation was the fact that the medical device was for in-house-use only or custom-made. These characteristics of the medical device are not asked for in the ABR-form. Respondents only sporadically indicated that they had been unaware of the obligation to notify IGJ. Most respondents to the enquiry showed awareness of the obligation and mentioned that they used information from IGJ and CCMO websites, standard operating procedures of their hospital and training courses for clinical investigators. However, the response rate to the CCMO enquiry among applicants was limited.

For the period 2015-June 2017, 63 studies were not notified to the IGJ, an average of 25 non-notified studies/year (38% of the total number of studies). Due to the notification lag time, this average could still decrease. For the period 2011-2013 the average number was 31 non-notified studies/year (56% of the total number of studies) according to a previous evaluation. The decreased average number of non-notified

studies is an indication that the measures for disseminating information had a positive effect on the notification rate.

Samenvatting

Dit rapport beschrijft een evaluatie van de naleving van de notificatieplicht voor klinisch onderzoek met medische hulpmiddelen. De uitvoering van klinische studies met medische hulpmiddelen moet voldoen aan de eisen zoals vastgelegd in Europese richtlijnen, richtsnoeren en standaarden. Op het niveau van de lidstaten zijn de Europese richtlijnen geïmplementeerd in de nationale wetgeving. In Nederland is de Inspectie voor Gezondheidszorg en Jeugd in oprichting (IGJ i.o.) de nationale bevoegde instantie voor klinisch onderzoek met medische hulpmiddelen. Daarnaast is de Centrale Commissie Mensgebonden Onderzoek (CCMO) de bevoegde instantie voor medisch-wetenschappelijk onderzoek met mensen. Wanneer het onderzoek valt onder de Wet Mensgebonden Onderzoek moeten klinische studies bij de CCMO worden aangemeld middels het Algemeen Beoordeling en Registratie formulier (ABR-formulier) en beoordeeld worden door een medisch-ethische toetsingscommissie (METC).

Na aanmelding bij de CCMO en positieve beoordeling van de METC, maar voor de start van de studie geldt voor bepaalde klinische studies met medische hulpmiddelen een notificatieplicht bij IGJ i.o.. Dit betreft klinisch onderzoek met niet- Conformité Européenne (CE) gemarkeerde medische hulpmiddelen en/of CE-gemarkeerde medische hulpmiddelen die CE gemarkeerd zijn voor andere doeleinden dan in het klinisch onderzoek. Afgelopen jaren hebben zowel de IGJ i.o. als de CCMO actief informatie over deze wettelijke verplichting verstrekt om de notificatiegraad te verbeteren. Om het effect van deze maatregelen om de informatie te verspreiden na te gaan heeft de IGJ i.o. het Rijksinstituut voor Volksgezondheid en Milieu (RIVM) de opdracht gegeven de notificatiegraad in de periode januari 2015- juni 2017 te onderzoeken.

In deze evaluatie heeft het RIVM gegevens van IGJ i.o. en CCMO vergeleken die betrekking hebben op klinische studies met medische hulpmiddelen, die zijn aangemeld en/of genotificeerd in januari 2015 – juni 2017. De vergelijking leverde een aantal klinische studies op die wel waren aangemeld bij de CCMO maar niet genotificeerd bij IGJ i.o..

Om de redenen voor het niet notificeren te achterhalen werd een CCMO enquête over notificatie bij IGJ i.o. gebruikt. De meest genoemde reden was dat het medisch hulpmiddel ‘alleen voor gebruik in de eigen instelling’ bedoeld was of ‘op maat gemaakt’ was. Deze karakteristieken worden niet gevraagd in het ABR-formulier. Respondenten noemden slechts in een enkel geval dat ze niet bekend waren met de notificatieplicht. De meeste respondenten waren wel bekend met de notificatieplicht en noemden als informatiebron hierover de websites van IGJ i.o. en CCMO, de standaardprocedures van hun ziekenhuis en cursussen voor klinisch onderzoekers. De respons op de navraag van de CCMO was echter laag.

In de periode 2015-juni 2017 werden 63 studies niet genotificeerd bij IGJ i.o., gemiddeld 25 niet-genotificeerde studies /jaar (38% van het

totale aantal studies). Vanwege de vertraging in notificatie kan dit gemiddelde nog dalen. In de periode 2011-2013 was volgens een eerdere evaluatie het gemiddelde 31 niet-genotificeerde studies/ jaar (56% van het totale aantal studies). Het gedaalde gemiddelde is een indicatie dat de maatregelen om informatie te verspreiden een positief effect hebben gehad op de notificatiegraad.

1 Introduction

1.1 Background

Clinical investigations (CIs) with medical devices have to be performed in accordance with European Directives (Medical Devices Directive and Active Implantable Medical Devices Directive), guidelines and standards. Each member state has implemented European Directives in national legislation. In the Netherlands, the European Medical Devices Directive and Active Implantable Medical Devices Directive are implemented in the Dutch Medical Devices Decree (Besluit medische hulpmiddelen (BMH)[1]) and the Dutch Active Implants Decree (Besluit actieve implantaten (BAI)[2]). In addition, the Dutch Medical Research Involving Human Subjects Act (Wet medisch-wetenschappelijk onderzoek met mensen (WMO)[3]) also applies to most of the clinical investigations with medical devices. All clinical investigations liable to the WMO must be registered at the Central Committee for Research Involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek (CCMO)) and reviewed by an accredited medical research ethics committee (Medisch-Ethische Toetsingscommissie (METC))[4]. The Health and Youth Care Inspectorate (IGJ) is the national competent authority (NCA) for clinical investigations with a medical device in the Netherlands[5].

In the Netherlands, a manufacturer can only perform a clinical investigation with a medical device or an active implantable medical device if the following criteria are met:

- There has to be a positive opinion from a METC;
- The manufacturer must have a valid liability insurance before the clinical investigation starts, to cover any harm caused by the clinical investigation;
- The manufacturer must notify the IGJ before the actual start of the clinical investigation.

These criteria are derived from the BMH (Article 13) and the BAI (Article 7). Several exceptions to the notification obligation exist. The IGJ does not need to be notified if a clinical investigation with a Conformité Européenne marked (CE-marked) medical device is used within the intended purpose for which CE marking was issued[6]. Notification is also not needed for a clinical investigation with a so-called in-house developed medical device. Such a medical device is developed in collaboration between doctors and technicians within the framework of clinical investigation at a healthcare institution and is not (yet) on the market. In such a case, the institution or technical department in question is not considered a manufacturer in the sense of the BMH or BAI. However as soon as a party delivers a non CE-marked medical

[1] Besluit medisch hulpmiddelen, http://wetten.overheid.nl/BWBR0007307
[2] Besluit actieve implantaten, http://wetten.overheid.nl/BWBR0006060
[3] Wet medisch wetenschappelijk onderzoek met mensen, http://wetten.overheid.nl/BWBR0009408
[4] In the remaining part of the report the term ethics committee will be used instead of medical research ethics committee
[5] See footnote 1 and 2 s
[6] See footnote 1 and 2

device to another (healthcare) institution, with the aim of doing clinical research as defined in the law, the investigation must be notified to the IGJ[7]. Clinical investigations with a custom made medical device for only one subject (n=1) are usually not notified. The term 'custom-made' is to be interpreted in a strict sense. Clinical investigations with customized medical devices or custom-made in series including a larger number of subjects (n>1) have to be notified.
After receiving the application form and all requested and mandatory information and having no additional questions, the IGJ will send a formal (written) acknowledgement to the applicant that the notification obligation under the decree has been fulfilled[8].

In 2014, the IGJ commissioned an evaluation of compliance to the current registration/notification obligations for the Netherlands in the period 2011-2013. An investigation conducted by the National Institute for Public Health and the Environment (RIVM) showed that applicants/sponsors of clinical investigations with medical devices were often unaware of the notification obligation to the IGJ[9]. Based on this evaluation IGJ took several dissemination measures, such as adapting the information on their website and organizing an invitational conference to inform all relevant stakeholders, on the notification procedure in order to improve the notification rate.

1.2 Aim of this study

In order to examine the impact of the measures to disseminate information on the notification procedure, IGJ commissioned the RIVM to evaluate the notification rate in the period January 2015- June 2017. For this evaluation, the RIVM examined:

1) whether registered clinical investigations with medical devices at the CCMO match with those clinical investigations notified to the IGJ.
2) whether clinical investigations with medical devices notified to the IGJ match with those clinical investigations registered at the CCMO.
3) the reason why clinical investigations were not notified to the IGJ after registration at the CCMO and what the characteristics of these non-notified clinical investigations are.

[7] http://www.ccmo.nl/en/research-with-a-medical-device
[8] http://www.igz.nl/english/medical_devices/clinical_research_involving_the_use_of_medical_devices/
[9] Roszek B, van de Laar CWE, Jongen PMJM (2013). Klinisch onderzoek met medische hulpmiddelen. Een foto van het veld anno 2012. Rijksinstituut voor Volksgezondheid en Milieu, Bilthoven. RIVM briefrapport 080012002 [confidential report in Dutch].

2 Methods

2.1 Study on registration and notification

Data sources
On request of the IGJ, the CCMO extracted records of clinical investigations registered from January 1st, 2015 to June 30th, 2017 from their CCMO administrative database, which encompasses all clinical investigations liable to the WMO. Input for this CCMO database comes from completed online General Assessment and Registration Forms (Dutch: ABR formulier), as filled in by the applicant of the clinical investigation. The RIVM considered these registered clinical investigations for analysis if they were initial applications, involved medical devices and had a positive opinion of the ethics committee (EC). Amendments to an application were excluded.

Concurrently, the IGJ created manually an overview of clinical investigations with medical devices notified from January 2015 till November 2017. This overview was based on documents submitted to the IGJ (in paper form or digitally), such as the EC's opinion, application form, or other documents. Notification at IGJ is required after assessment by the EC of the protocol and before the actual start of the clinical investigation. This means that the period between registration at the CCMO and notification to IGJ can be considerable. In this evaluation, notifications to IGJ were collected until 14 November 2017.

Information items used for the compilation by the CCMO and IGJ are presented in Table 2.1. Both data sets were saved in a separate Excel file and merged for further analysis. Individual clinical investigation records were checked for inconsistencies.

Exclusion criteria
Clinical investigations were excluded if they pertained to CE-marked medical devices (unless this was outside the intended purpose of the clinical investigation), in vitro diagnostic medical devices, or other types of interventions, e.g. medicinal products, vaccines, somatic cell therapy, radiopharmaceutical products.

In the IGJ data set, clinical investigations not covered by the WMO and investigations with duplicate ABR numbers were excluded.

Clinical investigations with registration-notification mismatch
Matching of clinical investigations was based on the ABR number. Matching was considered valid if a pair of ABR numbers could be identified and was, therefore, straightforward.

A mismatch was defined if an ABR number could only be found in one of both data sets. For clinical investigations notified to the IGJ but not included in the CCMO data set, the CCMO checked their administrative database to trace the investigation.

Table 2.1 Items used for the overview of clinical investigations

CCMO data set	*ABR question*
ABR number	
Version number of ABR form	
Date of assessment	
Status of ABR	
EudraCT number	B1b
Applicant – Type of organization/company	B5b
Applicant – Name of organization/company	B5b
Applicant – Name of contact person	B5a
Applicant employed at the sponsor	B6
Sponsor – Type of organization/company	B7
Sponsor – Name of organization/company	B7
Title of clinical investigation	C1a
Mono/multicentre clinical investigation, including countries	C6, C6a
Participating centre(s) – Type of centre	C9
Participating centre(s) – Name of centre	C9
Type of clinical investigation	C14
Medical device – Name	C17a
Medical device – Manufacturer	C17a
Medical device – CE mark	C17a
Medical device – Classification of medical device	C17a
Medical device – Advice of suitably qualified specialist within institution	C17a
Class(es) of condition addressed in clinical investigation	C21
Ethics committee – Name	I1 (?)
IGJ data set	
ABR number, if available	
Notification number (“WPM-nummer”)	
Date of notification	
Medical device – Name	
Medical device – Manufacturer, if available	
Contract research organization – Name, if applicable	
Ethics committee – Name, if available	
Remarks	

Additional information from applicants

Based on the resulting data set, the RIVM analysed which clinical investigations were (probably) subject to the notification obligation. For their enquiry on notification of clinical investigations to IGJ, the CCMO contacted applicants of these investigations by email. Applicants were asked whether they notified their clinical investigation to the IGJ (see Appendix I). An explanation was requested in case the clinical investigation was not notified to the IGJ. The applicants were also asked which source of information they used to determine if their clinical investigation needed to be notified or not and what their opinion was about the quality of the information received.

Data adjustment

Based on the information of responding applicants of the CCMO enquiry, a corrected inclusion of clinical investigations was performed (clinical investigations that did not need to be notified were excluded).

Classification of medical devices
The classification of medical devices used in the ABR form differs from the classification rules in accordance with the BMH. The classification as used in the ABR form is defined in an explanatory CCMO document[10]:

- Class I: generally includes most non-invasive medical devices.
- Class IIa and IIb: generally include most invasive medical devices.
- Class III: These are medical devices that are used in direct connection with the cardiovascular system or central nervous system.

Although class IIa and IIb medical devices are not separately defined, they can be distinguished in the ABR form. The classification as described in the ABR form was used for the data analysis and not manually adjusted in accordance with the classification rules in the BMH.

For non-matching clinical investigations involving class III medical devices, the name of the medical device as given in the ABR form was used to create product categories. Other information obtained from the manufacturer's website (e.g. clinical program) and the summary of the public ABR form were used to complement the categorization.

Data analysis
SPSS Version 24 (IBM Corporation, USA) was used for merging, matching and descriptive statistics, i.e. cross tables.

[10] Explanation of the general assessment and registration (ABR) form (version December 2015). http://www.ccmo.nl/attachments/files/b1-abr-toelichting-15-dec-2015-eng.pdf

3 Results of study on registration and notification

3.1 Matching of clinical investigations

Figure 3.1 summarizes the process by which the data set of clinical investigations with medical devices was created. For the period January 1st, 2015- June 30th 2017, 549 clinical investigations with medical devices were extracted from the CCMO database, which were included in the Excel file. Initially, 66% of these clinical investigations (361/549) were excluded based on one or multiple exclusion criteria. The majority of clinical investigations pertained to CE-marked medical devices (65%; 355/549), with fewer focusing on in-vitro diagnostic medical devices (0.7%, 4/549), and medicinal products (2.7%, 15/549). Notably, 3.3% (18/549) of the clinical investigations had a negative opinion of the ethics committee.

For 34% of the investigations (188/549), the notification obligation seemed applicable. These investigations were selected for the CCMO enquiry on notification to IGJ.

The CCMO could not complete their enquiry before the data collection closure of this evaluation on 14 November 2017. The result of the enquiry was that 145 of 188 initially included applicants received the enquiry and part of the included applicants (43/188) did not receive the enquiry. Among those receiving the enquiry, only part of the non-responders (17/60) did receive a reminder.

The actual response from applicants who did receive the CCMO enquiry was 59% (86 respondents of 145 addressed applicants; 43 of 188 applicants did not receive the enquiry; figure 3.1). Forty-nine responders stated that they notified their clinical investigation to the IGJ while 37 responders stated that they did not notify the IGJ. The majority of the responders, who did not notify the IGJ, stated that notification was not applicable because the medical device used in the investigation was only used in the own institution or was custom-made.

Based on the information provided, included investigations were corrected (see also Figure 3.1).

Finally, 162 registered clinical investigations were included for comparison with the IGJ data set. However, it should be noted that for a significant part of the included studies (54%; 102/188) no additional data could be obtained, either because of the applicants' non-response to the enquiry (n=59) or because the applicant did not receive the enquiry in time (n=43).

The total number of clinical investigations notified to the IGJ was 168 during the period 2015-2017. Of the 168 clinical investigations, 15.5% (26/168) were excluded and 84.5% (142/168) were included for comparison with the CCMO data set.

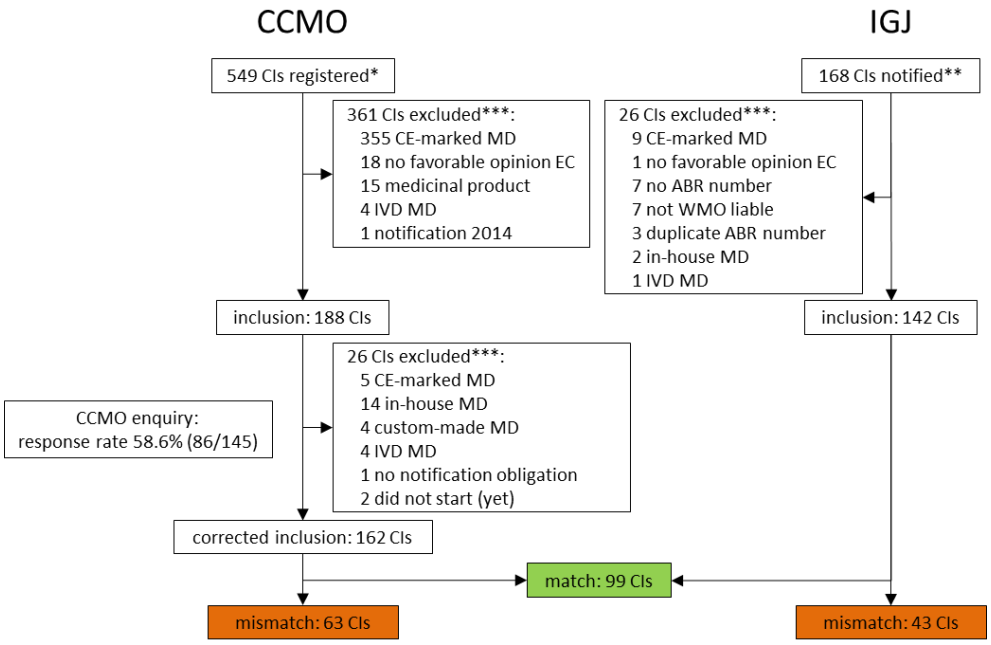

Figure 3.1 Flowchart of number of clinical investigations registered at the CCMO (left) or notified to the IGJ (right) during the period 2015-2017. Period of registration 2015-2016-first six months of 2017. ** Period of notification 2015-2016-first eleven months 2017. *** Clinical investigations could have multiple exclusion criteria with a maximum of two combinations.*

The CCMO and IGJ data matched for 99 clinical investigations that were both registered and notified (figure 3.1). In their response to the CCMO enquiry, the applicants from three of these matching studies stated that their study had not been notified to IGJ, which was incorrect. This finding relates to the fact that the manufacturer of the medical device is responsible for the notification, while often another party is the applicant for registration at the CCMO.

Data extraction from the CCMO database depends on the answers from the applicant provided in the completed ABR form. Due to this, a significant part of the clinical investigations notified at the IGJ (30%; 43/142) could not be identified in the initial CCMO data set. These studies had an ABR number, indicating that they were registered in the CCMO database, but not as an investigation with a medical device. For this reason, these investigations were not automatically extracted from the CCMO database. They had to be traced separately by hand in the CCMO database and were added to the CCMO data set. Furthermore, it is often incorrectly indicated whether a medical device has CE-marking or not in the ABR form, making it difficult to determine whether a clinical investigation has a notification obligation. This demonstrates that filling the ABR form correctly and completely is crucial for monitoring purposes.

The results below describe the non-notified clinical studies. No comparison is made with the clinical studies that were notified.

3.2 Non-notified clinical investigations

The number of clinical investigations with medical devices registered at the CCMO and not notified to the IGJ to be included in the evaluation (short: non-notified clinical investigations) was 63 (39%; 63/162; Figure 3.1). The total of included investigations was 162.

Non-notified clinical investigations were almost equally distributed over the investigated years 2015 till 2017 (Table 3.1). With a mismatch which was on average 39% per year. Most applicants of clinical investigations registered in the first half of 2017 did not receive the CCMO enquiry in time (91%; 42/46). Data of these investigations have therefore not been corrected by additional information. After the data collection closure on 14 November 2017, the IGJ received several notifications for studies in this category that could not be included in this evaluation.

Table 3.1 Number of included investigations and mismatches per year

	Included investigations	Mismatches	Mismatches
Year	n	n	%
2015	60	23	38,3
2016	55	21	38,2
2017[a]	47	19	40,4
Total	*162*	*63*	*38,9*

[a] First six months

For most non-notified clinical investigations, a university medical center was the sponsor (n=39, Table 3.2).

Table 3.2 Type of sponsor and year of registration of non-notified clinical investigations

	Year		
	2015	2016	2017[a]
Type of sponsor	n	n	n
University medical centre	14	15	10
Other hospital	7	3	2
Industry	2	1	2
Clinical research organization	.	1	.
University	.	1	5
Total	*23*	*21*	*19*

[a] First six months

The majority of non-notified clinical investigations were investigator-initiated investigations (87%, 55/63) in which a university medical centre (67%;37/55), a hospital (21%; 12/55) or a university (11%; 6/55) acts both as sponsor as well as applicant (Table 3.3).

Table 3.3 Type of sponsor and type of applicant of non-notified clinical investigations

	Type applicant						
Type of sponsor	CRO	GGZ	Industry	Other centre	Other hospital	UMC	University
Industry	3	.	1	1	.	.	.
Clinical research organization (CRO)	1	.	.	.	.	.	.
University medical centre (UMC)	.	1	.	.	.	37	1
University	.	.	.	.	.	.	6
Other hospital	.	.	.	.	12	.	.

The majority of non-notified clinical investigations (78%, 49/63) were conducted in one centre (Table 3.4). Multicentre clinical investigations were less frequent, with multiple sites in the Netherlands, in Europe or globally.

Table 3.4 Type of clinical investigations (mono/multicentre) and year of registration of non-notified clinical investigations

	Year		
	2015	2016	2017[a]
Type of clinical investigation	n	n	n
Monocentre, Netherlands	17	17	15
Multicentre, Netherlands	2	3	2
Multicentre, Europe	3	1	1
Multicentre, globally	1	.	1
Total	*23*	*21*	*19*

[a] First six months

All non-notified clinical investigations for which additional data were available concerned medical devices that had no CE-mark for the application intended in the investigation. A small number (n=20) of these medical devices were CE-marked for other applications, i.e. non-CE-marked for the intended purpose to be investigated, but CE-marked for intended purpose outside the scope of the clinical investigation (Table 3.5).

Table 3.5 Non-CE-marked medical devices and year of registration of non-matching clinical investigations registered at the CCMO

	Year		
	2015	2016	2017[a]
Type of non-CE-marked medical device	n	n	n
Non-CE-marked medical device	15	15	13
CE mark for other application	8	6	6
Total	*23*	*21*	*19*

[a] First six months

Medical devices are classified according to their risk profile. Class I (low risk medical devices) contained the largest number of mismatches compared to the other classes. Class IIb medical devices represent the group in which the least mismatches were found (Table 3.6). Product categories of class III medical devices are shown in Table 3.7.

Table 3.6 Classification of medical device and year of registration of non-notified clinical investigations registered at the CCMO

	Year		
	2015	2016	2017[a]
Classification of medical device*	n	n	n
Class I	7	11	11
Class IIa	10	7	5
Class IIb	1	3	1
Class III	5	.	2
Total	*23*	*21*	*19*

*Not adjusted to classification rules in accordance with BMH
[a] First six months

Table 3.7 Product categories of class III medical devices of non-notified clinical investigations registered at the CCMO*

	Number of clinical investigations
Product category	n
3D-printed clavicle reconstruction	1
Cardiac rhythm management device	1
Deep brain stimulation system (stimulator, lead)	2
Degradable bone cement	1
Drug infusion system	1
Resorbable surgical sealant	1
Total	*7*

*Not adjusted to classification rules in accordance with BMH

During the period 2015-2017, most non-notified clinical investigations involved neoplasms (benign, malignant and unspecified), nervous system disorders, psychiatric disorders, and gastrointestinal disorders. In conjunction with disorders, surgical and medical procedures were also often mentioned.

Dutch hospitals are divided into three different categories, namely university hospitals (in Dutch: academische ziekenhuizen), top clinical hospitals (in Dutch: topklinische ziekenhuizen) and general hospitals (in Dutch: algemene ziekenhuizen). From the 63 non-notified clinical investigations, 35 clinical investigations were conducted in one university hospital (Table 3.8). Seven studies were solely conducted in a top clinical hospital and only 4 studies were performed in a general hospital. Six studies were carried out by a university hospital that collaborates for this investigation with a top clinical hospital, a general hospital, a university or with a combination of these centres. In 10 studies, other organizations/centres than a hospital were involved in the clinical investigation.

*Table 3.8 Type of participating centres involved in non-notified clinical investigations**

Type of participating centre	Non-notified investigations (n)
Universityhospital	35
Top clinical hospital	7
General hospital	4
University hospital + topclinical hospital	3
University hospital + topclinical hospital + general hospital	2
University hospital + university	1
Other centre type	10
Clinical research organization	*1*
Mental healthcare (GGZ)	*1*
Rehabilitation centre	*2*
Organization, not specified	*1*
Dental practise	*1*
University	*4*
Unknown	1
Total	*63*

* These investigations can be mono or multicentre.

University hospitals are sponsor for the majority (39/63) of non-notified clinical investigations (table 3.9). Top clinical hospitals were the sponsor of six non-notified clinical investigations. One general hospital is the sponsor for four non-notified clinical investigations: the same general hospital is also the applicant of these investigations and the only participating centre. For the remaining 14 non-notified clinical investigations other organizations than hospitals were the sponsor.

Table 3.9 Type of sponsor for the non-notified clinical investigations

Type of sponsor	Non-notified investigations (n)
University hospital	39
Top clinical hospital	6
General hospital	4
Other centre type	14
Total	*63*

3.3 Response to enquiry

Of the 63 non-notified studies, 16 applicants (25%) responded to the CCMO enquiry, while the majority of applicants (75%; 47/63) did not respond. The 16 responses have been summarized in table 3.10. Seven applicants responded that the clinical investigation had been notified although these studies were not included in the IGJ data set and could not be traced by IGJ. Two of the responders did not notify the investigation to the IGJ because this was not their responsibility according to them. Three responders did not notify their clinical investigation to the IGJ because this procedure was unknown or unclear to them. Four applicants mentioned other reasons for non-notification.

Table 3.10 Responses applicants non-notified studies to CCMO enquiry

Study	Notified?	Reason for non-notification
1	No	Medical device only for research
2	Yes	
3	Yes	
4	Yes	
5	Yes	
6	No	Procedure unclear
7	No	Early closure study
8	No	Notification obligation unknown
9	No	Notification is task of another party
10	No	Pilot study in one single centre
11	No	Notification is task of another party
12	No	Medical device was not the study subject
13	Yes	
14	No	Notification obligation unknown
15	Yes	
16	Yes	

The applicants were also asked which source of information they used to determine whether their clinical investigation should be notified to the IGJ. Twenty-eight responders used information from solely IGJ, 24 responders used information from solely the CCMO and 18 responders used both information sources. Sixteen responders did not use the information of IGJ or CCMO to determine whether they needed to notify their clinical investigation. In general, the responders stated that the information of IGJ or CCMO was clear, accessible and sufficient (Table 3.11). These results might be biased since most of the responders notified clinical investigations or were aware of the exception rules. As explained before, among the non-responders, applicants of investigations that should have been notified were probably overrepresented.

Table 3.11 Overview of the information source the responders to the enquiry used and the quality of this information

Quality of available information	Information source		
	IGJ (n=28)	CCMO (n=24)	IGJ + CCMO (n=18)
Clear/Unclear	13/2	10/6	9/2
Accessible/ Not accessible	5/2	5/1	5/1
Sufficient/ Insufficient	11/3	11/3	4/1

The responders were also asked whether they had additional remarks on the notification process. A compilation of comments and suggestions is presented in textbox 3.1.

Textbox 3.1 Comments and suggestions from applicants responding to CCMO enquiry

Comments:

- The clinical investigation is probably notified to the IGJ by the METC or CCMO but this is unclear to me.
- How to deal with the role of the manufacturer in a research consortium (national/international). (2x)
- There is no manufacturer. It is therefore unclear if a notification is needed.
- Infrastructure on website is unclear/not logical (mainly at CCMO).
- Term notification is confusing. It sounds like you only need to inform but you need approval from the IGJ. (2x)

Suggestions:

- Link the CCMO and IGJ. This prevents double work and delays. (4x)
- Additional information from the CCMO could lead to a faster notification at the IGJ. (2x)
- Place a simple flowchart on the websites of CCMO/IGJ about the notification procedure.
- Indicate that IGJ must be notified when an ABR form is completed.
- Add examples. This makes it more clear for the product designers and researchers to which category their product belongs and which procedure should be initiated.
- Add a link to the IGJ and CCMO on the webpages of the METCs.
- State on the website that the IGJ has the possibility to require changes to a document after approval of the METC.

4 Discussion and conclusion

For the period 2015-June 2017, 63 studies were found to have been registered to the CCMO but not (yet) notified to IGJ by 14 November 2017. This is an average of 25 non-notified studies/year (38% of the total number of studies). It should be noted that notification to IGJ occurs often sometime after registration at the CCMO (i.e. there is a time lag). After the data-collection closure on 14 November 2017, clinical investigations registered in the first half of 2017 (or even in 2016) could still be notified to the IGJ. If these notifications are done before the start of the investigation, they are still in time from a legal point of view.

This report describes several characteristics of non-notified clinical investigations. It should be noted that these characteristics were not identified for the notified clinical investigations and that a comparison between notified and non-notified investigations was not made. For instance, the fact that the majority of non-notified investigations were monocentre studies does not mean per se that monocenter investigations are notified worse than other investigations. It could also mean that there are in total more monocentre than multicentre clinical investigations with medical devices.

For the non-notified clinical investigations, it is also possible that exemptions to the notification obligation are applicable or that the investigational medical device is CE marked before starting the clinical investigation. Checking and adjusting data on these aspects requires direct information from the applicants. However, checking the non-notified clinical investigations is complicated. For legal reasons, neither IGJ nor RIVM were able to contact directly the applicants of clinical trials for research purposes and the results of the CCMO enquiry on investigations with medical devices had to be used as data source. The enquiry could not be finished during this evaluation, which means that part of the applicants of included investigations from 2017 did not receive the enquiry before data collection closure of this evaluation. Furthermore, the response to the enquiry was rather low and part of the non-responders did not receive a reminder.

Both the time lag in notification after registration and the difficulties in data collection hindered a reliable assessment of the exact notification rate in 2015-2017. Nevertheless, the results indicate that a significant number of clinical investigations are not notified to IGJ despite the legal obligation. The enquiry also revealed that several applicants had a wrong assumption about the notification status of their investigation. Some applicants stated that another party was responsible for notification. These responses show that confusion on notification exists, which argues for adaptation of the ABR form in order to facilitate applicants in complying correctly with the notification obligation.

On the other hand, the answers of the applicants responding to the CCMO enquiry combined with the increasing number of notifications in 2015-2017 compared with the period 2011-2013 also reflect the efforts

to disseminate information on the notification procedure over the past years. Most of the responding applicants indicated that the information on the notification procedure is sufficient and clear. The websites of both IGJ and CCMO are the major information sources. Furthermore, information on the procedure is also embedded in Stand Operating Procedures of several academic hospitals and in professional courses on clinical investigations nowadays. Applicants also highly appreciate direct and helpful communication with the IGJ.

Data extraction from the CCMO database with respect to medical devices is difficult to conduct comprehensively. For monitoring clinical investigations with medical devices, the completeness and correctness of the information in the ABR form according to the CCMO guideline is crucial[11]. Some suggestions for improvement are:

- The ABR form could be evaluated by the CCMO, IGJ and other interested parties for clarity with respect to clinical investigations with medical devices. For example, it could be helpful for applicants if a reminder of the obligation to notify at the IGJ would pop-up.
- The filled ABR forms could be checked more intensively on correct information at the start of the registration procedure. The ethics committees could pay specific attention to the information provided with respect to the medical devices investigated.

Conclusion

This evaluation indicates that non-compliance to the notification obligation exists. For the period 2015-June 2017, 63 studies remained in the category non-notified after the CCMO enquiry (status 14 November 2017). This is an average of 25 non-notified studies/year (38% of the total number of studies). However, this average could still decrease due to the notification time lag. The evaluation conducted in 2014 for the period 2011-2013 revealed an average of 31 non-notified studies/year (56% of the total number of studies), indicating that the measures for disseminating information had a positive effect on the notification rate.

Confusion about the notification status and a significant number of non-notified investigations demonstrate that practical and easily accessible information on the notification procedure will remain important for enhancing compliance. Ongoing dissemination of information and linking the information of both the IGJ and CCMO websites is very helpful for applicants, especially in view of changing EU regulations. Furthermore, the possibility to contact directly IGJ with questions is highly valued and should be continued.

[11] http://www.ccmo.nl/attachments/files/ccmo-richtlijn-abr-formulier-7-2-2014-doc.pdf

5 List of abbreviations

ABR	General Assessment and Registration (Algemeen Beoordeling en Registratie)
BAI	Dutch Active Implants Decree (Besluit actieve implantaten)
BMH	Dutch Medical Device Decree (Besluit medische hulpmiddelen)
CCMO	Central Committee for Research Involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek)
CE	Conformité Européenne
CI	Clinical Investigation
EC	Ethics Committee
IGJ	Health and Youth Care Inspectorate (Inspectie Gezondheidszorg en Jeugd i.o.). Name of the inspectorate from 1 November 2017.
IGZ	Dutch Healthcare Inspectorate (Inspectie voor de Gezondheidszorg). Former name of the inspectorate until 1 November 2017 and used in the enquiry.
IVD	In Vitro Diagnostic
MD	Medical Device
METC	Medical Research ethics committee (Medisch-Ethische Toetsingscommissie)
NCA	National competent authority
RIVM	National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu)
UMC	University Medical Center
WMO	Dutch Medical Research Involving Human Subjects Act (Wet medisch-wetenschappelijk onderzoek met mensen)

6 Appendix I: Enquiry

Information request to applicant in Dutch

Geachte heer / mevrouw,

Hierbij verzoek ik u om de gegevens aan te vullen van een door u bij een METC ingediend klinisch onderzoek naar een medisch hulpmiddel.

De CCMO registreert het medisch-wetenschappelijk onderzoek in Nederland op basis van het ABR-formulier en rapporteert hierover. Op dit moment vraagt het ABR-formulier echter nog geen informatie over de notificatie bij de Inspectie voor de Gezondheidszorg (IGZ) van klinische studies naar medische hulpmiddelen. Het Besluit medische hulpmiddelen eist dat de fabrikant klinische studies naar medische hulpmiddelen die (nog) geen CE-markering hebben of die een CE markering hebben voor een andere toepassing, notificeert aan IGZ.
Om meer inzicht te krijgen of de studies genotificeerd worden en of de informatie over de notificatie toereikend is, wil de CCMO de gegevens van klinische studies met medische hulpmiddelen in de periode 2015-eerste helft 2017 aanvullen met informatie over de notificatie. De CCMO zal de aanvullende gegevens geanonimiseerd delen met IGZ. Doel is om te bekijken of de huidige informatievoorziening over klinische studies met medische hulpmiddelen aan fabrikanten en/of onderzoekers adequaat is. De aanvullende gegevens worden niet gebruikt in het kader van handhaving door IGZ.

De CCMO verzoekt u voor de volgende studie aanvullende gegevens te verstrekken via het bijgevoegde antwoordformulier:

ABR nummer studie	Click here to enter text.

U kunt het antwoordformulier binnen twee weken na ontvangst van deze e-mail ingevuld en ondertekend zenden aan:
notificaties@ccmo.nl

Mocht u vragen hebben over dit verzoek, dan kunt u contact opnemen met het secretariaat van de CCMO middels bovenstaand email adres of per telefoon (070-346700).

Bij voorbaat dank voor uw medewerking.

Met vriendelijke groet,

Dr. C. de Heer
Algemeen Secretaris
CCMO

ANTWOORDFORMULIER
Extra gegevens studie naar medisch hulpmiddel

ABR nummer studie	Click here to enter text.

Aanvullende gegevens

Vraag	Antwoord
1.Is bovenstaande studie genotificeerd bij de Inspectie voor de Gezondheidszorg?	☐JA, namelijk door ☐Door indiener van de studie bij METC/CCMO ☐Door de fabrikant van het medisch hulpmiddel ☐Door de verrichter/opdrachtgever van de klinische studie (sponsor) ☐Door de uitvoerder/onderzoeker van de klinische studie (investigator) ☐Anders, namelijk: Click here to enter text. ☐NEE
Indien antwoord JA op vraag 1, ga verder met vraag 3 t/m 5 Indien antwoord NEE op vraag 1, ga verder met vraag 2 t/m 5	
2. Indien NEE bij vraag 1: wat is de reden dat de studie niet is genotificeerd? *Meerdere antwoorden mogelijk*	☐Notificatieplicht niet van toepassing voor deze studie. Kruis hieronder aan waarom dit niet van toepassing is: ☐Voor start van de studie kreeg het medische hulpmiddel CE-markering voor de toepassing ☐Het medisch hulpmiddel is custom-made (‘naar maat gemaakt’) ☐Het medisch hulpmiddel is binnen dezelfde instelling ontwikkeld als waar de studie plaatsvindt en wordt niet elders toegepast ☐De studie is later geamendeerd, waardoor notificatie niet van toepassing ☐Anders namelijk: Click here to enter text. ☐Notificatie is taak van andere partij ☐Onduidelijk of notificatieplicht van toepassing is voor deze studie ☐De studie is/wordt niet gestart

	☐Notificatieplicht was mij niet bekend ☐Reden onbekend ☐Anders namelijk: Click here to enter text.
3. Welke informatiebron gebruikt u om te bepalen of uw klinische studie aangemeld moet worden bij IGZ?	☐Geen ☐ (Webpagina) IGZ ☐(Webpagina) CCMO ☐Anders namelijk: Click here to enter text.
4. Wat vindt u van de informatie verkregen via deze informatiebron? (Bij deze vraag kunnen meerdere antwoorden van toepassing zijn)	☐Duidelijk ☐Onduidelijk ☐Toegankelijk ☐Niet toegankelijk ☐Voldoende informatie beschikbaar ☐Onvoldoende informatie beschikbaar ☐Anders namelijk: Click here to enter text.
5. Heeft u aanvullende opmerkingen over de notificatieprocedure?	

Naam indiener:
Click here to enter text.

Plaats, datum:
Click here to enter text.

Naam indiener:

Plaats, datum:

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