Standard Operating Procedure	SOP No: 003 Version: 1.0 Effective Date: 01 Jan 2021

Title: Accredited Ethics Committee (aEC) and Competent Authorities (CA) review and reporting procedures via Pedmed-NL

Purpose	To explain the review and reporting procedure for scientific research that falls within the Medical Research Involving Human Subjects Act in the paediatric population executed via Pedmed-NL
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PURPOSE

To explain the review and reporting procedures for scientific research that falls within the research with human subjects act (in Dutch WMO) if executed via Pedmed-NL services; the national hub for the Netherlands.

APPLICATION

This SOP applies to all scientific "WMO" research in the paediatric population conducted in the Netherlands, for which the EC review and reporting procedures have been outsourced to Pedmed-NL

ABBREVIATIONS AND DEFINITIONS

Abbreviations

ABR	General Assessment and Registration (form)
AE	Adverse Event
aEC	Accredited Ethical Committee
BROK	Basic course for clinical investigators
c4c project	conect4children (collaborative Network for European Clinical Trials for children)
CA	Competent Authority
CBG	College ter Beoordeling van Geneesmiddelen
CCMO	Central Committee on Research Involving Human Subjects
CDA	Confidentiality Disclosure Agreement
CMO	Commissie Mensgebonden Onderzoek (MREC region Arnhem-Nijmegen)
CRF	Case Report Form
CRO	Clinical Research Organization
CTA	Clinical Trial Application
CSFQ	Center Specific Feasibility Questionnaire
C-TMF	Central Trial Master File
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
DSMC	Data Safety Monitoring Committee
DSUR	Development Safety Update Report
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EU	European Union
EudraCT	European union drug regulating authorities Clinical Trials
GCP	Good Clinical Practice (see ICH-GCP)
GDPR	General Data Protection Regulation (in Dutch: Algemene Verordening Gegevensbescherming (AVG)).
IB	Investigator Brochure
IC	Informed Consent

ICH-GCP	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP)
ISF	Investigator's Site File
Lareb	Dutch Registration and evaluation of adverse drug reactions (Netherlands Pharmacovigilance Centre)
LF	Local Feasibility
LPLV	Last Patient Last Visit
MREC	Medical Research Ethics Committee
NFU	The Netherlands Federation of University Medical Centers
NTR	Netherlands Trial Registry
PI	Principal Investigator
RC	Review Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SPoC	Single Point of Contact
SSFQ	Study Specific Feasibility Questionnaire
SOP	Standard Operating Procedures
SPC	Summary of Product Characteristics
S-TMF	Site Trial Master File
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TO	ToetsingOnline
VWS	Ministerie van Volksgezondheid, Welzijn en Sport/The Ministry of Health, Welfare and Sport
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch Wetenschappelijk Onderzoek met mensen)
WI	Work Instruction

Definitions

Amendment	Adjustment of a document or process
Applicant	An academic group / Sponsor or industry Sponsor or an intermediary appointed by a Sponsor that submits a request for feasibility assessment
Blinding	The aim of blinding is to ensure that the study participant who is taking part in the clinical scientific research and the treating physician are unaware of which treatment the study participant is receiving, in order to prevent any unwanted bias of the study data that are recorded.
Competent Authority	CCMO or Ministry of Health, Welfare and Sport
c4c	collaborative Network for European clinical trials for children
CRF	A case report form is a paper or electronic document (eCRF) specifically used in clinical research. The case report form is the tool used by the sponsor of the study to collect data from each participating patient.

CRO	A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions
Deblinding	Termination of the blinding should not be performed unnecessarily or unintentionally. During a study deblinding may only be performed in emergencies and for the reasons listed in the study protocol (per protocol). If it is a blinded study, then the investigator must record any premature breaking of the code on the study product(s) immediately and must declare this to the sponsor (e.g. unintentional breaking of the code, breaking of the code due to an SAE). In addition, deblinding will take place upon completion of the data collection in order to perform the final analysis.
Double-blind	Usually means that the study participants(s), investigator(s), monitor and in some cases the data analysts, do not know which treatment(s) were assigned to which study participant(s).
Non-substantial amendment	A minor adjustment of study documents or processes which do not have to be reviewed by the Independent Review Board (MEC or CCMO). It usually takes note of small changes, such as text corrections.
Off-label use	Use of a medical drug or device in a way that differs from the intended use defined by the manufacturer.
Partner sites	Sites that have signed the Pedmed-NL consortium agreement
Pedmed-NL	Dutch network for clinical trials in children
PI	Responsible leader of a team of individuals at the trial site where the clinical trial will be conducted
Protocol amendment	A written description of a change or a formal clarification of the protocol.
Randomisation	The process of assigning study participants to treatment or control groups by means of arbitrary (random) allocation, to rule out any subjective influence.
Single-blind	Usually means that the study participant(s) is/are not informed on the kind of treatment (placebo/study treatment) they receive.
Site	Location where trial-related activities are actually conducted
SOP	Detailed, written instructions to achieve uniformity of the performance of a specific function
SPoC	The centralised electronic point of entry into c4c for sponsors/applicants, managed by the Network Infrastructure Office
Sponsor	An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial
Substantial amendment	An amendment is substantial if the change has a significant impact on: the patient safety, scientific value, execution or supervision of the study, quality or safety of the study product, risk/benefit analysis. Also considered substantial: change of sponsor or principal investigator. A positive judgement must be obtained from the Independent Review Board before a substantial amendment can be implemented.
Testing Committee	Evaluating ethics committee (approved MEC or CCMO)

CONTENTS

This SOP describes the review and reporting procedure prior to, during and at the end of scientific research that falls within the "WMO" in the paediatric population. Almost all scientific research with human subjects must be assessed by an accredited ethics committee (aEC), see the Flow chart for obtaining Approval from the aEC. In all these cases, the research may only start after a positive assessment from the aEC has been obtained.

In addition, "WMO" drug-related research and a certain type of medical device research must also be submitted to the competent authority.

Finally, local approval from the Executive Board of the hospital where the study will be conducted, must be obtained.

1. OVERVIEW OF ASSESSMENT ORGANIZATIONS

A paediatric study, for which the EC review and reporting procedures have been outsourced to Pedmed-NL, must be submitted to three types of assessment organizations, i.e.: 1. An accredited ethical committee, 2. A competent authority, 3. The Executive Board from each participating site.

1.1 Review committee

The following review committees are distinguished: Medical Research Ethics Committee (MREC), e.g. CMO Arnhem-Nijmegen region and CCMO. See the link to determine which review committee is applicable to the study.

CCMO

In the case of certain types of research the legislator chose to combine expertise in one single committee. This concerns the review of research with specific ethical, legal or social aspects and research in fields with limited expertise. The review of these types of research has been appointed to the Central Committee on Research Involving Human Subjects (CCMO) in the Central Review of Medical Research Involving Human Subjects Decree.
If the protocol is to be submitted to the CCMO, the procedure as described on the website of the CCMO is to be followed. The CCMO also offers a large number of templates of documents in the research dossier on their website. The CCMO does not charge a fee for its review.

MREC (Medical Research Ethics Committee)

Research that does not need to be reviewed by the CCMO, must be reviewed on medical-ethical grounds by a legally accredited MREC. The CMO Arnhem-Nijmegen region is a recognized MREC, where most of the WMO-compliant research for which the EC review and reporting procedures have been outsourced to Pedmed-NL, will be assessed.

The assessment of the submission file by an MREC may involve costs. No national agreements have been made about the amount. The exact rates can be requested from the review committee concerned. An MREC can transfer the file to the CCMO when it deems necessary.

1.2 Competent authority

In all drug research and certain medical device research the research proposal must also be assessed by the competent authority. The competent authority will assess whether there are "motivated objections" to the conduct of the study. No costs are charged by the competent authority for the

marginal assessment. The submission to the competent authority and the review committee may occur simultaneously. The party that serves as competent authority depends on the type of research and the review committee. See also flow chart below.

Competent authority in drug research
The competent authority checks the European databank on adverse effects (EudraVigilance) for previously reported adverse drug reactions that lead to unacceptable risks to the research participant.

The CCMO is the competent authority when MREC is the review committee. Registration is possible via the website. The Ministry of Health, Welfare and Sport (VWS) is the competent authority when CCMO is the review committee. Registration is possible via the website.

1.3 Executive Board
In the Netherlands all WMO-compliant research requires local approval from the Executive Board of the participating sites to a clinical trial. This is called the Local Feasibility review (in Dutch, Toets Lokale Uitvoerbaarheid). It is possible that a site is charging a fee for the local feasibility. The procedure for local approval is different in each site.

2. METHODS

1. Pedmed-NL receives aEC/CA review request from Sponsor (Please check the work instruction 'EC review' for a more detailed workflow).
2. Pedmed-NL confirms receipt and acceptance of review request to Sponsor
3. Pedmed-NL provides an authorization letter and send this letter to the Sponsor for signing
4. Pedmed-NL compiles the required standard research file. (More information can be found on the CCMO website
5. Pedmed-NL submits the research file to the aEC, according to the procedure applicable to the review committee (for CMO Arnhem-Nijmegen see instructions) (Meeting dates CMO Arnhem-Nijmegen)
6. If applicable, also submits the submission file to the competent authority at the same time.
7. Pedmed-NL receives first reaction from aEC
8. Pedmed-NL informs Sponsor about first reaction of the aEC and asks the Sponsor to respond to any questions from the aEC.
9. Pedmed-NL submits answers received from Sponsor to aEC
10. Checking of answers by aEC
11. When the study is approved, Pedmed-NL receives positive judgement from aEC.
12. Pedmed-NL informs Sponsor on aEC/CA approval
13. Pedmed-NL ensures that all necessary documents for local approval go to the participating sites.
14. Start study after approval of local Executive Board, within the period stipulated in the approval letter from the review committee and inform the review committee of the definitive start date of the study. The study start date is the date on which the first research participant signs the informed consent form.
15. If there is a change in the study after the initial approval of the review committee, Pedmed-NL (authorized by the Sponsor) must submit an amendment (See work instruction for more details) to the review committee beforehand. If it is a substantial amendment, it must be evaluated by the review committee and the competent authority, if applicable. A non-substantial amendment must be offered to the review committee for notification. An

administrative change is not seen as an amendment. (For CMO Arnhem-Nijmegen see instructions)

16. Substantial protocol violations (critical deviations in the execution of the protocol, see examples on the CMO Arnhem-Nijmegen website (in Dutch)) must be reported immediately to the review committee, by the Sponsor. Pedmed-NL can provide support by referring the Sponsor or coordinating PI to the correct procedure.
17. If applicable, the safety reports (occasional and periodic overviews of adverse effects: SAEs and SUSARs must be reported to the review committee. If applicable, they must also be reported to the competent authority by the Sponsor. Pedmed-NL can provide support by referring the Sponsor or coordinating PI to the correct procedure.
18. If applicable, the reports from DSMB should be reported to the review committee, by the Sponsor. Pedmed-NL can provide support by referring the Sponsor or coordinating PI to the correct procedure.
19. Once a year, the Sponsor must send a progress report to the review committee, unless the positive assessment states that this must be more frequently. The first report should be provided digitally one year after the start of the research, by the Sponsor. Pedmed-NL can provide support by referring the Sponsor or coordinating PI to the correct procedure.
20. After the last research participant (in the Netherlands) is out of the study, the Sponsor must complete the termination study notification form and submit it to the review committee. If applicable, it should also be reported to the competent authority (see CCMO).
21. As soon as available, the Sponsor should send a final report with concluding report/manuscript to the review committee.

3. RESPONSIBILITIES

The Sponsor has the final responsibility for:

- The delivery of the required documents for the research file to Pedmed-NL
- Signing letter of authorization
- Submitting the safety reports, DSMB report, progress report to the aEC/CA
- Submitting the termination study notification form at the end of the study to the aEC/CA

Pedmed-NL has the final responsibility for:

- Compiling the research file
- Collecting all required documents
- Translating all involved patient material and information forms
- Completing the ABR form and upload it to ToetsingOnline
- Corresponding with sponsor and participating sites
- Submitting the research file to the MREC and if applicable the CA
- Preparing required documents for approval of the Executive Board, for each participating site

Responsibilities of the participating sites:

- Send the required site-specific documents to Pedmed-NL
- Obtaining approval of the Executive Board of each participating site

The review committee has final responsibility for:

- The assessment of the research file within the statutory deadlines.

REFERENCES

Directive 2001/20/EC of the European Parliament and of the Council

Dutch Law Medical Research Involving Human Subjects Act (WMO; *Wet medisch-wetenschappelijk onderzoek met mensen*)

CCMO External Review Directive

Medical Research (Human Subjects) Compulsory Insurance Decree

(Note: These documents can be found at http://www.ccmo.nl.)