STANDARDS FOR NON-INTERVENTIONAL STUDIES WITH MEDICINES INITIATED BY PHARMACEUTICAL COMPANIES

Introduction

Healthcare benefits from legitimate and responsible medical-scientific research. For research that falls under the Dutch *Medical Research Involving Human Subjects Act* (Wet medisch-wetenschappelijk onderzoek met mensen = WMO), legal standards have been established. For research that does not fall under this law (non-WMO studies), no specific legal requirements apply. In consultation with stakeholders, the standards described below have been established to ensure that such *non-WMO* research is carried out for legitimate reasons and in a proper way. These standards aim to provide a framework for those who initiate the study, for those who assess the legitimacy of the study and those who conduct the study.
Standards for reviewing non-WMO studies are basically no different than for WMO, albeit that nuances can be different. In fact, all non-WMO studies should be risk-free from a medical point of view. After all, if there are medical risks associated with the study, the study falls under the WMO. This does not alter the fact that other types of risks are more prominent in non-WMO studies. Undesirable sales-inducing aspects, for example, can play a prominent role for medicines that are already on the market, while this will be less of a problem for drugs that are still in the pre-registration phase. On the other hand, risks in the area of methodology, privacy and consent of participants/patients or no publication/transparency of study results occur in both non-WMO and WMO research. This framework of standards will not capture all risks, exclude them and weigh them against any benefits of the study. Also, participants may experience some minor burden. Performing reliable and legitimate non-WMO research therefore remains a joint responsibility of initiators, assessors and executing healthcare professionals.

WMO or non-WMO?

A. Criteria for WMO research

1. It concerns medical/scientific research and

2. Participants are subject to procedures or are required to follow behavioral rules

The website of the CCMO describes the criteria that a study must meet in order to be covered by the WMO (http://www.ccmo.nl/en/your-research-does-it-fall-under-the-wmo)

B. Criteria for non-WMO study:

1. It concerns medical/scientific research and

2. Participants are NOT subjected to any procedures nor are behavioural rules imposed on them (participants receive regular care)

3. The medicines regulation makes a distinction between research (trial) and study. Not every study can therefore be categorized as a "trial". One can think of registers in which patient data are collected, patient satisfaction surveys, pilot study into the feasibility of a research parameter, etc. Such studies with drugs are not in scope of the regulation, but should be reviewed by the framework for non-WMO studies.

C. Other laws and responsible behavior (self-regulation)

The WGBO (*Act on the Medical Treatment Agreement*) and the AVG (*General Directive for Protection of Personal Data*) are still applicable for clinical research with medicines, even if the Dutch *Medical Research Involving Human Subjects Act* (WMO) does not apply.
Despite the applicable laws or self-regulatory Codes like the Code for Pharmaceutical Advertising (CGR), Code of Good Practice and Code of Good Conduct (where the strictest code prevails), license holders (pharmaceutical companies) and healthcare professionals must apply responsible behavior towards each other, also during the conduct of this type of studies. This responsibility applies in particular in order to protect the interests of patients and public health in general.

Standards for non-WMO studies with medicines initiated by license holders (pharmaceutical companies).

The following criteria apply for non-WMO studies:

A. General

1. The WMO does not apply for the study (in the future: the Regulation for Clinical Trials with Medicines)
   a. the study qualifies as Medical Scientific Research (as described in the WMO)
   b. participants are NOT subjected to any procedures nor are behavioural rules imposed on them (participants receive regular care).

2. It is a study with medicines.

3. The study is sponsored and initiated by a pharmaceutical company ('license holder').

4. The medicinal product is registered in the Netherlands for the indication and treatment regime used in the study.

When a pharmaceutical company is the initiator of the non-WMO study with medicines, the medicine must be prescribed according to the registered indication, administration and dosage. If a company initiates or sponsors a non-WMO study with an off-label use, this may lead to unacceptable promotion of the relevant medicine.

5. Participation in the non-WMO study must not be the reason for the prescription of the investigated medicine.

Prior to the study, the HCP and the participant should already have agreed on the chosen treatment. This applies to both *de novo* patients and patients who are already being treated with a different medicine for the relevant condition.

No 'waiting period' is required since this could introduce a bias, for example early side effects could be missed in a study of side effects.

6. Applicable treatment guidelines, costs or positioning of the medicine are out of scope of the review.

7. The study is ethical with the Declaration of Helsinki as guiding principle.

The review assesses the non-WMO study on the standards as described in this document, not the feasibility in a specific institute.

In the event that a medicine in de study is provided temporarily or partially free of charge, it is strongly advised to ask the CGR in advance about its admissibility in the planned study.

B. Methodology, privacy, end of study, information and publication

8. The research question is relevant and unambiguously formulated, including primary and possible secondary endpoints

9. The design of the study is such that the research question can be answered, including:
    a. clearly defined statistical methods
    b. the sample size must match the research question and chosen methodology; too few participants will not lead to an outcome, too many participants imposes an unnecessary burden on the participants and could introduce undesirable promotional effects.

10. Data that are not relevant for the research question should not be collected or stored.

It is not the task of the review committee to improve the methodology of the study, marginal suggestions can be made for improvement, but if there are doubts about the methodology, a negative opinion will be given or it will be suggested that the study be withdrawn.

11. It should be clear for the participants of the study what is requested of them during which period.

12. The privacy of the participants is guaranteed, the following questions are answered positively:
    a. is the coding and processing of the data of the participants correct?
    b. is a procedure for informing the participant on chance findings established?
    c. are links between data files organized according to applicable laws and regulations?

One should follow the standards that apply in the institute or practice for the Protection of Personal Data. The GDPR (effective as of May 25, 2018) requires additional measures for the processing of personal data of the participants. Regarding privacy, the same rules apply to WMO and non-WMO studies.

13. The participant is sufficiently informed about the participation in the study and a written consent requested.

14. The study results must be made public.

15. Within 56 days (8 weeks) the Advisory Committee should be informed about the formal date the study ends in the Netherlands, as defined in the protocol. In most cases this is the date of the last measurement in the last patient entered in the study. In international studies, the start and end date of the study can differ per participating country.

16. In case the study is ended prematurely the Advisory Committee should be notified of the reasons within 15 days.

17. All study related documents must be archived for at least 15 years.

C. Financial agreements

18. Following precautions are taken in order to eliminate any sales incentives:
    a. Fee for Service (FFS) is based on the fair market value for the persons who actually perform the services and reimbursement of cost are within the norms as set by the CGR and endorsed by the Inspectorate;
    b. All study agreements are recorded in a written agreement, such as (not limitative):
        i. Description of provided services by HCO/HCP
        ii. Description of type of services per performing service provider
        iii. Applicable FFS per performing service provider
        iv. Realistic estimate of time spent per provided service
        v. Study period
    c. Employees of the scientific department of the license holder should perform pre-study or monitoring visits.
    d. Study documents cannot be promotional.

Based on the above-mentioned standards, one should be able to establish whether performing the study is legitimate. Furthermore, one should establish based on these standards, whether the payments for the study are reasonable in relation to the work performed in the context of the study. In particular fees represent a risk of undesirable sales-inducing incentives. The CGR has set maximum tariffs that can be paid to HCPs when they provide legitimate services (directly or indirectly) on behalf of pharmaceutical companies. These maximum rates are also used by the Health Care Inspectorate (Inspectie voor de Gezondheidszorg - IGZ). The structure of the planned fees consists of four elements: 1) services provided, 2) executor per service provided, 3) realistic estimate of the time required for execution of the service, 4) the maximum hourly rate per executor. In addition, any related reasonable expenses can be reimbursed. This must be clearly stated in the application. A table in which to enter these costs has been made available for this purpose (to be found on the website www.nwmostudies.nl). The time spent per service provided must be a realistic estimate. If during the execution of the investigation it appears that the estimate is not correct, it can be adjusted based on the current situation. The maximum hourly rates cannot be adjusted. It is the responsibility of the initiator and executors (practitioners and research institute) that the reimbursement does not give rise to unwanted incentives.
In addition to reimbursements, non-WMO investigations may include other, unintentionally, sales-promoting incentives. For example, participation in a study can be given a promotional character when it is brought to the attention of healthcare professionals by commercial employees of the company. The research documents can also have a promotional appearance when they are executed like promotional material for medicines, for example through color and image use, paper quality or shape.
Furthermore, participants in non-WMO studies with medicines cannot be reimbursed for their participation.
Finally, equipment or other items needed for the research can be made available, but may not be donated.

D. Submission request

19. All relevant documents must be submitted together with the application form.

20. Discrepancies between the submitted documents are excluded.

When a study that has been reviewed by the independent Review committee and received a positive advice, one can assume that the study meets the standards for non-interventional studies as described above.