Conditional inclusion procedure for orphan drugs, conditionals and exceptionals

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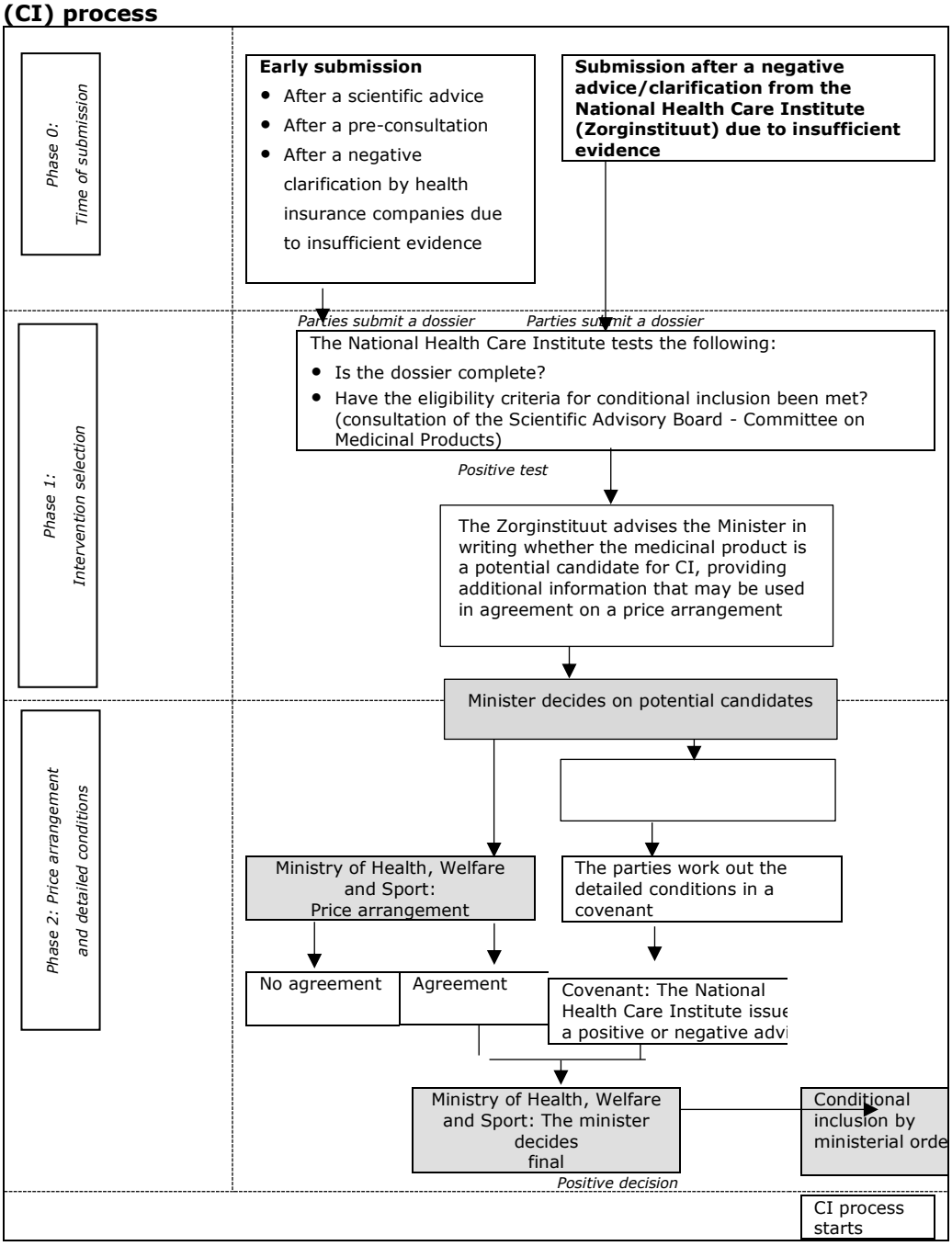
1.0	*27 August 2019*	*Original.*
2.0	*29 September 2023*	*Amendments following the first evaluation of the procedure (2022).*

Conditional inclusion procedure for medicinal products

1.1 Procedure for the start of the conditional inclusion process for medicinal products

Figure 1 outlines the procedure up to the conditional inclusion of a medicinal product. In the following sections, we will explain the various phases in more detail.

Figure 1: Flowchart - procedure for the start of the conditional inclusion (CI) process



1.1.1 *Scope*

Only the following medicinal products are eligible for the policy on conditional inclusion of orphan drugs, conditionals and exceptionals:

- registered medicinal products designated by the EMA as an orphan drug for the indication concerned;
- registered medicinal products for the indication concerned that have been given marketing authorisation by the EMA under certain conditions (so-called conditionals); and
- registered medicinal products for the indication concerned that have been given marketing authorisation by the EMA *under exceptional circumstances* (so-called exceptionals*).*

In addition, all medicinal products submitted for conditional inclusion must fulfil a *unmet medical need*.

1.1.2 *Phase 0: Time of submission*

The timing of the submission of a conditional inclusion dossier may vary:
- Scenario 1) Early submission prior to an assessment by the National Health Care Institute (Zorginstituut) or after a negative clarification[1] by health insurance companies due to insufficient evidence; or
- Scenario 2) Submission following a negative advice from or clarification of the National Health Care Institute due to insufficient evidence.

Scenario 1) Early submission

There are two moments at which the National Health Care Institute may inform marketing authorisation holders about the possibility of an early submission:

a. During the scientific advice.

In its scientific advice, the National Health Care Institute may give advice on the comparator, clinically relevant outcome measures, the required study duration and sub-groups (PICOt[2]). This will contribute to optimising the reimbursement dossier, which will help prevent delays later on in the process, e.g. due to the absence of essential data. No rights can be derived from a scientific advice. The National Health Care Institute bases its opinions on 'established medical science and medical practice', as well as applicable guidelines. Therefore, the National Health Care Institute cannot give any guarantees with regard to the final decision, but it can point out to every marketing authorisation holder of an EMA-designated orphan drug, conditional or exceptional the possibility of applying for conditional inclusion as soon as the final EPAR has been published. In doing so, the submitter will waive the standard assessment process of the National Health Care Institute.

b. During the pre-consultation.

The marketing authorisation holder can compile a preliminary reimbursement dossier and submit it to the National Health Care Institute as soon as the CHMP[3] has issued a positive opinion. The purpose of the pre-consultation is to ensure that the reimbursement dossier is as complete as possible. Based on the claim of the marketing authorisation holder, the National Health Care Institute will advise which data should be included in the dossier. During the pre-consultation, the National Health Care Institute will point out points of special interest to the applicant, such as the interchangeability, therapeutic value and cost-effectiveness of the medicinal product. The National Health Care Institute will also call attention to possible pitfalls.

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[1] Checking against current laws and legislation whether care is an insured provision within the framework of the basic package. Involves the assessment of compliance with established medical science and medical practice.

[2] PICO(t) stands for Population, Intervention, Comparison, Outcome and time.

[3] This is an EMA committee: Committee for Medicinal Products for Human use.

Now, the National Health Care Institute will also point out to every marketing authorisation holder of an EMA-designated orphan drug, conditional or exceptional the possibility of applying for conditional inclusion early, namely as soon as the final EPAR has been published. In doing so, the submitter will waive the standard assessment process of the National Health Care Institute.

In some cases, health insurance companies may express a negative clarification on an EMA-designated orphan drug, conditional or exceptional due to insufficient evidence. When that happens, marketing authorisation holders have the option to submit an early application for conditional inclusion to the National Health Care Institute.

In scenario 1, the marketing authorisation holder decides whether to follow the standard assessment process or to submit early. During an exploratory discussion, the National Health Care Institute advises the marketing authorisation holder on the most logical or pragmatic route. If the evidence gap is not (completely) clear, the National Health Care Institute recommends conducting a regular assessment. In that case, if the evidence gap has been clarified, an early submission for CI may be made after the discussion of the pharmacotherapeutic draft report in the WAR. Opting for early submission does not guarantee that the medicinal product in question will be conditionally included in the basic health care package.

Scenario 2) Submission following a negative advice from or negative clarification of the National Health Care Institute due to insufficient evidence.
If the National Health Care Institute issues a negative advice or clarification because there is insufficient evidence which cannot answer the 'package question[4]', the National Health Care Institute it will point out to the marketing authorisation holder the possibility of applying for conditional inclusion.

Following a negative advice from or clarification of the National Health Care Institute, parties must submit a dossier as soon as possible, to prevent the identified lack of evidence from becoming outdated as a result of new developments.

1.1.3 *Phase 1: Intervention selection*

Phase 1 starts when the dossier is submitted to the National Health Care Institute[5]. In this phase, the National Health Care Institute determines whether the medicine is suitable for conditional inclusion on the basis of the submitted dossier. This section will first discuss the criteria that a medicinal product must meet to be selected as a potential candidate for conditional inclusion. If the submitted medicinal product does not meet these criteria, it is not suitable for conditional inclusion and the policy for conditional inclusion can therefore not be deemed to apply to it. The selection procedure used by the National Health Care Institute, in consultation with the Scientific Advisory Board's Committee on Medicinal Products (Dutch: WAR-CG), is based on five criteria, which are explained in greater detail below.

1.1.3.1 Criteria

The National Health Care Institute has five criteria for assessing whether a medicinal product is eligible for conditional inclusion:

1 Has the medicinal product in question been granted marketing authorisation by the EMA and is it a designated orphan drug, conditional or exceptional for the

[4] The question as to whether the medicinal product in question can be included in the basic health care package.

[5] Please note: the dossier must be complete at the time of submission. Incomplete dossiers will not be processed. The Zorginstituut will not provide any missing information itself. The completeness of dossiers is assessed on the basis of the dossier requirements set out in Annex 1.

indication concerned?

2 Does the medicinal product in question fulfil an *unmet medical need*, according to the EMA definition?
3 Is the marketing authorisation holder the lead applicant? Are the co-applicants independent research institutes, professional groups and patient associations?
4 Is it plausible that the data collected through the proposed study will prove that the medicinal product in question warrants inclusion in the basic health care package?
5 Is it plausible that the package question will be answered within the period of conditional inclusion (max. 7 or 14 years)?

If the answer to any of the above questions is 'no', the medicinal product in question is not eligible for conditional inclusion.

Criteria 2,3,4 and 5 are explained in more detail below.

Explanatory notes - unmet medical need
This policy is intended for EMA-authorised orphan drugs, conditionals and exceptionals for unmet medical needs. The EMA defines an *unmet medical need* as[6] a condition for which there exists no satisfactory method of diagnosis, prevention or treatment, or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected. However, in some cases, alternative medicinal products may have been introduced in time between marketing authorisation by the EMA, the assessment by the National Health Care Institute/health insurance companies and the submission of a conditional inclusion dossier. As a result, the decision as to whether the medicinal product meets an unmet medical need may change. Therefore, when selecting medicinal products, the National Health Care Institute will in any case check whether an alternative treatment for the same condition has been introduced in accordance with established medical science and medical practice. If this is not the case, the National Health Care Institute will deem the medical need in question to be unmet at the time the medicinal product is submitted for conditional inclusion. Since medicinal products that are conditionally included in the basic health care package do not (yet) meet the legal criteria of the established medical science and medical practice, several medicinal products for the same indication may follow the CI procedure at the same time.

Conditional inclusion procedures are tailor-made. If, according to parties, there is an unmet medical need (in a subset of patients) – despite this not being mentioned in the EPAR and/or an alternative product has been introduced, in the time between market registration and application for CI or during the CI, that meets the legal criterion of the established medical science and medical practice – it is up to the professional and patient associations to substantiate why there is still an unmet medical need. The National Health Care Institute then tests this argument. However, improved ease of use compared to another treatment for the same indication that already complies with medical science and medical pratice in itself is insufficient to conclude that for (a subset of) patients there is an unmet medical need. There should then be evidence that the improved ease of use provides a significant therapeutic benefit for affected patients (more favourable or less unfavourable clinically relevant effects).

Explanation notes - requirements pertaining to the applicants behind the conditional inclusion dossier

[6] Article 4(2) of Regulation (EC) No 507/2006

The marketing authorisation holder must submit the conditional inclusion dossier to the National Health Care Institute together with an independent research institute and the relevant professional group and patient associations. It is important that the marketing registration holder is the lead applicant, because the Ministry of Health, Welfare and Sport will open negotiations with said holder about a discounted price during the period that the drug is conditionally included in the basic health care package at a later stage. In addition, it is important that the dossier is co-submitted by an independent research institute or centre of expertise and the relevant professional group and patient associations. The independent research institute will be responsible for conducting the study. The occupational group will, in cooperation with the patient association and the marketing authorisation holder, be primarily responsible for formulating key outcome measures and agreements on appropriate use. The marketing authorisation holder must include this information in the research proposal. If one of the above-mentioned parties chooses not to co-apply, the intervention in question will not be considered eligible for conditional inclusion, as this may demonstrate insufficient urgency or a lack of promise on the part of the medicinal product in question.

Explanatory notes - research proposal
The proposed research must meet several requirements. The criteria for the research proposal are listed in Annex 1. It is important to take into account that, at the end of the conditional inclusion process, the applicants must also submit a budget impact analysis and, possibly, a pharmaco-economic analysis. The National Health Care Institute will not process incomplete dossiers.

1.1.3.2 Feasible research

The purpose of conditional inclusion policy is to answer the package question for orphan drugs, conditionals and exceptionals that fulfil an unmet medical need. The National Health Care Institute will assess the submitted PICOt and any special characteristics to determine what would constitute appropriate research. This will differ from one medicinal product to the next. As a guidance, the National Health Care Institute has developed the appropriate research questionnaire[7]. Based on this questionnaire (see the appendix to the Established medical science and medical practice report (Stand van de Wetenschap en Praktijk, 2015)[8]), the National Health Care Institute will determine which elements are necessary and feasible to assess the effectiveness of the medicinal product. In doing so, the National Health Care Institute will examine the relevant patient population, the intervention, alternative treatment methods, relevant outcome measures and the duration of the study (PICOt) for the medicinal product in question. The National Health Care Institute uses this questionnaire to assess whether it is necessary and possible to use randomisation, blinding and a control group in the study.

The medicinal products to which this policy applies often have special characteristics, which may complicate randomisation and blinding. In some cases, for instance, it may be unethical to treat patients with a placebo. In other cases, there may not be any good predictors for the outcomes of the intervention and the actual outcomes may only be measured in the distant future.
In these cases, the National Health Care Institute will consider other research methods. Here are three examples:

- It may be possible to conduct an unblinded study. This is a plausible option if the outcome measures are unlikely to be affected by this study design (e.g. when measuring mortality). Uncontrolled studies, such as single-arm studies

[7] Zorginstituut. Appropriate research questionnaire. 2013

[8] Zorginstituut. Established medical science and medical practice report. 2015

are also possible, and the results obtained by these studies may be compared with a historical control group comparable to the group of treated patients.
- Another option could be to use an existing register to chart the natural course of the disease and compare this to the outcomes observed in treated patients.
- For conditions affecting a small, heterogeneous patient group, where it is difficult to determine clinically relevant outcome measures, a multi-tiered study design may be a valid approach in the short term. This may be an option if, for example, only some of the patients are expected to respond to the intervention and it is not yet clear which patients this will be. By setting up a sound register and applying start-and-stop criteria, such a multi-tiered approach may make it possible to define a sub-group for which the package question can be answered. In such a study, it is particularly important to make clear agreements about relevant values for outcome measures that give rise to the continuation of treatment.

As such, the National Health Care Institute will assess on a case-by-case basis whether the results that are likely to follow from the research design in question will be of sufficient quality to determine whether or not the intervention is in line with established medical science and medical practice at the end of the conditional inclusion process.

The National Health Care Institute has established that the dossiers submitted for inclusion in the basic health care package require an increasingly tailored approach. In an internal project, the National Health Care Institute will investigate how current technological and scientific developments can be integrated in the package management process. The results of this project will be applied to the conditional inclusion process at a later date.

1.1.3.3 Ongoing studies

For conditionals, as well as for some orphan drugs and exceptionals, the EMA requires prospective marketing authorisation holders to conduct additional studies for the purpose of context of marketing authorisation. As a result, there may already be ongoing (international) studies that can answer the question as to whether the medicinal product in question can be included in the basic health care package ("the package question"). If this is the question and the study results can be extrapolated to the Dutch situation, the research criteria can be deemed to have been met. If possible, Dutch patients can be included in this ongoing (international) study.

1.1.3.4 Broad access to research and the medicinal product

The National Health Care Institute proposes that patients who wish to use the medicinal product that will be reimbursed as soon as it is included in the basic health care package must participate in a study on said medicinal product. In the past, it has been shown that giving patients access to the medicinal product without requiring them to participate in the study leads to delays in the study. As such, if a patient can be included in the study but refuses to participate, they will not be eligible to receive reimbursement. If a patient enrols in the study initially but exits prematurely, they will no longer be eligible to receive reimbursement.
Over time, patients may no longer be able to participate in the main study because the required number of patients has already been reached. In order to ensure that the medicinal product remains broadly accessible for the entire duration of the conditional inclusion process, the National Health Care Institute requires applicants to set up at least as secondary supporting register study. This register study may be set up separately or may be linked to an independent (international) register. In this

context, it is important that the professional group or centres of expertise start collecting data for the following purposes:

- obtaining data about the cost-effectiveness and overall effectiveness of the intervention in practice. For example, for the formulation of start-and-stop criteria, optimising the dosage and identifying sub-groups for which the medicinal product in question could be of added value;
- evaluating the use of the medicinal product in domestic or international practice.

Access to the medicinal product is safeguarded by requiring researchers to include patients in a register, as a minimum requirement, should the main study be full. This also promotes the expedient use of the medicinal product in the future and enables us to better manage any future risks with regard to the basic insurance package.

1.1.3.5 Appropriate use

It is important to conditionally include in the basic health care package orphan drugs, conditionals and exceptionals that are eligible for conditional inclusion in a responsible manner. For this reason, the National Health Care Institute believes it is necessary that applicants specify how appropriate use will be promoted in the research proposal. From the orphan drug programme, we know of three instruments to guarantee the appropriate use of medicinal products: an indication committee, start-and-stop criteria, and the inclusion of treatment outcomes in a register. The research proposal must clearly indicate how these instruments are applied and how accountability is organised.

This method allows for the identification of other sub-groups that may benefit from the medicinal product or the evaluation of the required treatment duration or dosage to optimise the use of the medicinal product (appropriate use).

The parties, including at least the professional group and patient association, must determine which type of register will be of added value to the study prior to submitting the dossier. This will differ from one case to the next and must be specified in the research proposal. In any case, the National Health Care Institute considers it important that registers are disease-specific, independent, preferably Europe-wide and as simple as possible, and that an independent research institute is given access to the anonymised raw data.

In the case of expensive (ultra-) orphan drugs with a highly uncertain degree of effectiveness, it is particularly necessary to collect data on a European level in order to paint a clearer picture of the effects of the intervention. This also has great added value for conditionals and exceptionals. Medical specialists are responsible for entering data into the register, and patients are responsible for helping the researchers obtain the required data, e.g. by participating in tests and filling in questionnaires.

1.1.3.6 Explanatory notes - duration of study

The duration of the conditional inclusion process should be as short as possible.[9] When applying for conditional inclusion, the applicants must provide a detailed justification of the study duration required to answer the package question. Depending on the required duration, medicinal products will qualify for either category 1 (≤ 7 year) or category 2 (≤14 year).

[9] The period of conditional inclusion runs from the start of the study (i.e. inclusion, treatment, follow-up and analysis) up to and including the 6 months the Zorginstituut needs to prepare its advisory report on the therapeutic value of the medicinal product or its opinion on 'the state of science and practice'. Declarations of intent from participating centres, a final decision from the Central Committee on Research Involving Human Subjects (Dutch: METC), the assessment of the sponsor or consortium agreement and similar documents must have been obtained prior to starting the conditional inclusion process.

Category 1: Medicinal products for which the package question is expected to be answered within seven years are eligible for inclusion in category 1. At the end of the predetermined required study duration, including the assessment of the National Health Care Institute, the period of conditional inclusion will come to an end and the National Health Care Institute will decide whether to include the medicinal product in question in the basic health care package, the 'package decision':
(1) the product exits the conditional inclusion process and is included in the basic health care package;
(2) the product exits the conditional inclusion process and is not included in the basic health care package.
Six months before the end of the predetermined required study duration, the marketing authorisation holder shall submit a reimbursement dossier to the National Health Care Institute. The National Health Care Institute will assess the dossier and issue a final package advice or clarification on whether or not the medicinal product merits inclusion in the basic health care package.

Category 2: for example, for medicinal products for conditions with a slow, progressive course, it will take longer to demonstrate clinically relevant effects on hard outcome measures. As a result, it may also take longer to answer the package question. In order to give such medicinal products the chance to prove themselves and complete the conditional inclusion process, the National Health Care Institute recommends that the process may last longer than seven years under exceptional circumstances and strict conditions. Naturally, the overall aim is always to restrict the duration of the study to a minimum. For this reason, applicants who believe that they will need more than seven years must provide sound reasoning as to why this is the case and explain how likely it is that an extended process of conditional inclusion will answer the package question. In order to ensure that the study remains feasible, a maximum duration of fourteen years applies. It is undesirable for the situation to arise in which there is no clear information about the effectiveness of a medicinal product even after the predetermined required study duration. In order to prevent such a situation from arising, fixed go/no-go moments will be scheduled in addition to the yearly monitoring process for all medicinal products in category 2. During these moments, the National Health Care Institute will evaluate the medicinal product on the basis of predetermined interim outcome measures specified by the professional group. The outcome of this interim review may be that:
(1) the conditional inclusion process is continued *(go*); or
(2) the conditional inclusion process is discontinued and the medicinal product is not included in the basic health care package *(no go*).
The number of *go/no-go* moments and the intervals between them will depend on the PICOt and the predetermined interim outcome measures. This, too, will differ from one case to the next. If the conditional inclusion process is continued after each *go/no-go* moment, the conditional inclusion in category 2 will come to an end after the predetermined required study duration. The National Health Care Institute will subsequently decide whether or not to include the medicinal product in the basic health care package, leading to one of the following outcomes:
(1) the product exits the conditional inclusion process and is included in the basic health care package;
(2) the product exits the conditional inclusion process and is not included in the basic health care package.
Six months before the end of the predetermined required study duration, the marketing authorisation holder shall submit a reimbursement dossier to the National Health Care Institute, which will then issue a final advisory report or clarification on whether or not the medicinal product merits inclusion in the basic health care package.

The National Health Care Institute will monitor the progress of studies in both categories on an annual basis (see section 2.2.1).

The Minister has asked whether it would be desirable to allow for a one-off extension. The National Health Care Institute takes the view that this is, in principle, not desirable. This can only be considered in exceptional circumstances. For example, if a CI procedure is already ongoing for a certain indication and a second product is conditionally admitted to the basic health care package for the same indication. This may have an impact on patient inclusion, especially with orphan drugs. In that case, the National Health Care Institute can advise the Minister to grant an interim extension of the CI.

1.1.3.7 Selection procedure

Prior to submitting a research proposal, the applicants can schedule a meeting with the National Health Care Institute to discuss matters that are relevant to the medicinal product in question. These matters may include:
- formulating the PICOt (emphasising the patient population, interim and final outcome measures and the required study duration);
- clinical relevance of the effect;
- sub-groups;
- start-and-stop criteria;
- the presence of an expertise centre;
- indication committee;
- availability of domestic and international registers.

Many of these matters are fundamental elements of the research proposals submitted by the parties to the National Health Care Institute. The applicants are responsible for recording these relevant matters in a meeting report.
After the meeting, the marketing authorisation holder can submit a conditional inclusion dossier to the National Health Care Institute. Based on this dossier, the National Health Care Institute will assess whether the medicinal product in question qualifies for conditional inclusion. The National Health Care Institute will submit the dossier, including its own considerations, to the Medicinal Product Committee of the Scientific Advisory Board (WAR-CG). The research proposal will be discussed in the WAR-CG committee meeting, with a focus on the PICOt and the feasible information trajectory (FIT) questionnaire. Subsequently, the applicants will receive a draft advisory report on their research proposal from the National Health Care Institute, including any *go/no-go* moments, if applicable. If necessary, the applicants will be given the opportunity to modify their research proposal and resubmit the changed version. This will then be followed by a second reading by the WAR-CG, followed by a final advisory report about the research proposal. Only dossiers including an approved research proposal will be allowed to continue to the next stage of the process.

If all selection criteria are met, the National Health Care Institute will advise the Minister in writing that the medicinal product in question is a potential candidate for conditional inclusion. This report is usually limited to a single medicinal product. With an early submission procedure (scenario 1), it will take approximately six months for the National Health Care Institute to prepare its adviseory report. Dossiers following a negative advice from or a negative clarification of the National Health Care Institute due to insufficient evidence (scenario 2) are expected to have a lead time of within four months. In such cases, there will be no need to assess the therapeutic value of the medicinal product (extramural) or whether it is in line with established medical science and medical practice (intramural), as this will already have been done in the advisory report or clarification. However, if the CI file is submitted more than six months after the negative advice or the negative

clarification by the National Health Care Institute, it may take longer to prepare the advisory report. In this situation, it should be examined whether the evidence gap previously determined by the National Health Care institute is still valid. In that case, we strive for a maximum lead time of six months.

In the event that the maximum budget for conditionally included medicinal products has already been reached, any additional medicinal products still eligible for conditional inclusion will be placed on a waiting list.

1.1.4 *Phase 2: Price arrangement and preparing a detailed covenant*

Phase 2 starts when the National Health Care Institute informs the Minister that a medicinal product is a potential candidate for conditional inclusion. The Ministry of Health, Welfare and Sport contacting with the marketing authorisation holder to come to a financial arrangement. The parties (marketing authorisation holder, professional groups and patient organisations) will further develop the conditions in greater detail and lay them down in a covenant signed by all parties. The Ministry of Health, Welfare and Sport and the National Health Care Institute will not be signatories of the covenant.

1.1.4.1 Price arrangement

More and more medicinal products are being launched that were backed up by relatively less evidence when the authorisation was granted. The idea behind the accelerated marketing authorisation procedure is that using medicinal products in practice can help ensure that the patients who need them the most can access them more quickly. In addition, practical usage data can help speed up the overall development of the medicinal product. This raises an important dilemma, in that it means that the continued development of medicinal products is financed from public funds more often than before, whereas, traditionally, the marketing authorisation holder would pay the costs for using the product during the research phase. As such, these are solid grounds for reducing the entry reimbursement amount for such products. After all, it is not yet clear whether the medicinal product complies with the established medical science and medical practice. Due to the special status of the upcoming marketing authorization, prospective marketing authorisation holders must be aware that a price arrangement will have to be agreed to prior to the conditional inclusion. All costs other than those for the medicinal product, e.g. the costs of the study for conditional authorisation, will remain payable by the marketing authorisation holder.

Note: A medicinal product shall only be eligible for conditional inclusion if the Ministry of Health, Welfare and Sport and the marketing authorisation holder agree on a price. Another precondition for conditional inclusion in the basic health care package is that the total unit price of the medicinal product be made public.

To provide the Ministry of Health, Welfare and Sport with the necessary information regarding the price arrangement, the National Health Care Institute will provide the following information:

1) Patient numbers;
2) List price ;
3) Dosage information.

Explanatory notes - international patient data

The National Health Care Institute will report to the Minister whether the marketing authorisation holder will provide access to international patient data for the independent research institute. Access to these data can only be granted if the marketing authorisation holder has access or will be given access to these data.

These international patient data may help answer the package question with a greater degree of certainty, which is why the availability of said data is considered a plus.

1.1.4.2 Preparation of a detailed covenant

It is important to make clear-cut agreements and arrangements before the start of the conditional inclusion process, in order to prevent disputes from arising between patients and researchers, for instance, if the conditional inclusion process is discontinued. To this end, the covenant must contain at least the following elements:

1) the main points put forward in the research proposal (including interim outcome measures for category 2 products);
2) any publications resulting from the project must be published immediately and made freely available via open access;
3) data files resulting from the project must comply with FAIR data principles;
4) agreements on patient information, which involves informing patients that treatment with the medicinal product in question will be reimbursed temporarily in the context of further research into the product, although it will be made available to a broad group of patients for the duration of said research;
5) the exit strategy;
6) the de-implementation plan;
7) the commitment that in the event of a future CI request for a competitive medicinal product, the parties will collaborate to find the best solution for the patient. In some cases, this may mean that two competing products follow the CI procedure together;
8) annexes: the research proposal and the report of the meeting with the National Health Care Institute about matters relevant to the medicinal product in question.

Explanatory notes - open access publications and FAIR data principles

The results of projects involving medicinal products financed with public funds must be made publicly available. Applicants for conditional inclusion will therefore be required to ensure that all publications resulting from the project are published immediately and made freely available via open access. They are also required to share data files resulting from the project in accordance with FAIR data principles.

Covenant launch meeting

The marketing authorisation holder, professional groups and patient associations are responsible for the success of the conditional inclusion process. They will therefore have to develop the conditions themselves and ensure that consensus is reached.[10] The National Health Care Institute can, however, be of assistance in this phase by providing advice, for instance. This is why the National Health Care Institute will seek to organise a meeting with all applicants. Depending on the subject, other parties could be involved in this phase as well. In addition, the National Health Care Institute will assess whether the draft covenant offers sufficient guarantees for the appropriate implementation and completion of the conditional inclusion process (see the above-mentioned 8 mandatory parts of the covenant). If any additions to or modifications of the covenant are required, the National Health Care Institute will discuss this with the applicants.

Preferably, phase 2 should last no more than 6 months (except for the period

[10] In this procedure, the National Health Care Institute advises the Minister of VWS independently and is therefore as least possible part of the process as possible. To safeguard this independence, the National Health Care Institute is not a party in the signing of the covenant.

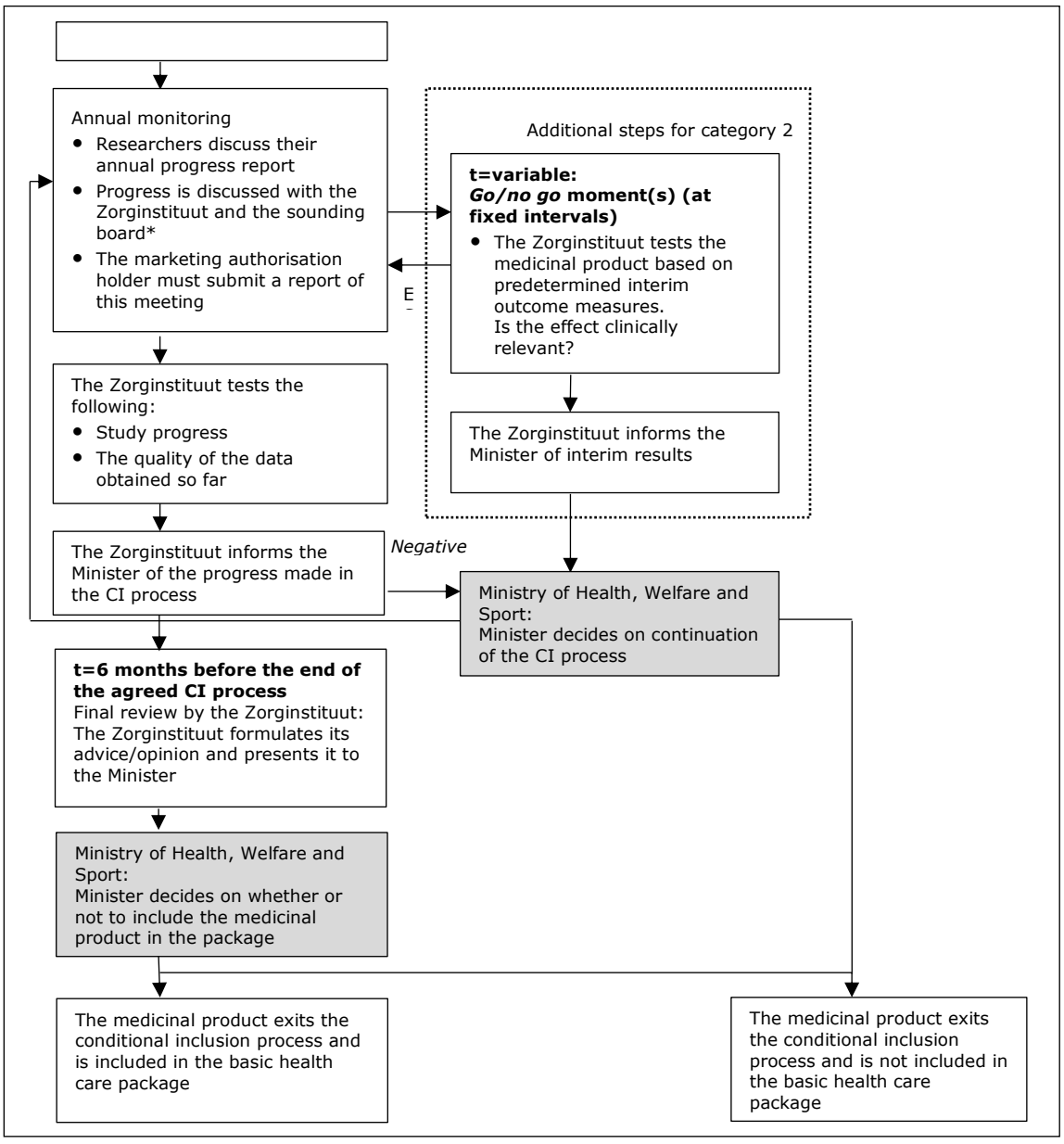
necessary to reach a price arrangement). In the opinion of the National Health Care Institute, extending this period makes little sense. If no consensus can be reached within six months, it is possible that the parties may not be on the same page, or that the development of the medicinal product in question is not urgent or promising enough. Moreover, developments in the medical industry move rapidly, so as time passes, the chances increase that the research proposal will be obsolete or outdated. To achieve the six-month lead time, it is important that after the potential candidates have been appointed, the parties immediately start drafting the covenant and that the Ministry of Health, Welfare and Sport starts discussions on a price arrangement as soon as possible. To this end, the National Health Care Institute informs the Ministry of Health, Welfare and Sport in good time that a potential candidate may be joining.
In phase 2, the applicants may also submit their proposal to the Medical Research Ethics Committee (Dutch: METC).

After all parties sign the covenant, the National Health Care Institute will present it to the Minister, and give advice on whether or not to start the conditional inclusion process based on the agreements made in the covenant.

1.2 Procedure during conditional inclusion

Figure 2 outlines the procedure during the conditional inclusion of a medicinal product. The following sections will describe the various stages of the conditional inclusion process in greater detail.

Figure 2: Flowchart of the procedure followed during a conditional inclusion (CI) process



ıe sounding board shall consist of representatives of all stakeholders involved in the covenant.

1.2.1 *Annual monitoring during the conditional inclusion process*

Once a year, the marketing authorisation holder will organise a meeting to discuss the progress and relevant interim findings of the studies with the sounding board. The sounding board shall consist of representatives of all stakeholders involved in the covenant. The representative of the National Health Care Institute will serve as an observer in said meetings.
Prior to these meetings, the researchers must submit a progress report to the National Health Care Institute. The report and findings stated in it must be transparent, comprehensible and verifiable, and contain at least the following information:

- compliance with the agreements set out in the covenant;
- number of participating centres;
- are the initial stakeholders still involved?
- how is the inclusion of the main study progressing?
- is there still consensus on the outcome measures studied within the professional group?
- can the parties prove that the registers are kept up to date?
- completeness of data registration;
- number of patients included per centre;
- protocol changes (if any).

In addition, the parties will evaluate the following:

- relevant domestic and international developments regarding the effectiveness of the conditionally included medicinal product;
- has an alternative treatment method become available that is in line with established medical science and medical practice? In other words, is there still an unmet medical need?
- should the start-and-stop criteria be updated based on scientific evidence and/or register data?

The marketing authorisation holder is responsible for drawing up reports on the meetings of the sounding board.
Based on the progress reports and the discussions about these reports in the sounding board meetings, the National Health Care Institute will track the progress of the studies and the quality of the data obtained so far. Every year, the National Health Care Institute will prepare a brief report to the Minister on the progress of the conditional inclusion project and advise on the continuation of conditional inclusion. At the request of the National Health Care Institute, the parties involved in the project shall provide the up-to-date information needed to draw up this annual report.

Based on the annual monitoring moments, the National Health Care Institute will assess the progress of the project based on the inclusion and feasibility of the research process and advise the Minister on whether or not to allow the research process to continue. Based on the information provided, the Minister may, on procedural grounds, terminate the conditional process prematurely, such as in the event of slow inclusion, a failed follow-up study, the registration of an alternative intervention in line with established medical science and medical practice, or the publication of other data that necessitate the premature termination of the study or the conditionally included medicinal product. The committee responsible for approving the research protocol (the Medical Research Ethics Committee or the Central Committee of Medical Research on Human Subjects) may, in principle, decide to terminate studies for medical and ethical reasons at its own discretion.

If unexpected problems arise with regard to the studies, the agreements about the studies included in the covenant, or the conditional inclusion process, the parties involved must report this to the National Health Care Institute immediately.

1.2.2 Interim *go/no go assessment* on inclusion of a medicinal product in category 2

In addition to the annual monitoring process, the National Health Care Institute will also assess whether category 2 medicinal products are still promising, whether they have a clinically relevant effect on interim outcome measures and whether the study may still answer the question as to whether the medicinal product in question answers the package question.
The National Health Care Institute will base its interim reviews of category-2 medicinal products on the pre-agreed interim outcome measures. The National Health Care Institute will also assess the progress of the study and determine whether the medicinal product in question has a clinically relevant effect. If the medicinal product is shown to be insufficiently effective with regard to the pre-agreed interim outcome measures, the National Health Care Institute will advise the Minister accordingly, who may then decide to terminate the conditional inclusion process prematurely. This will automatically start the de-implementation process.

1.3 Final assessment

The marketing authorisation holder must submit a dossier to the National Health Care Institute no later than six months before the end of the period of conditional inclusion. This dossier must contain at least the following components:

a. the results of the main study, preferably as a published, *peer-reviewed* manuscript or in any other format that can easily be analysed;[11]
b. the results of the register study in a format that can be analysed by the independent research institute;
c. an updated version of the systematic review on the effectiveness of the medicinal product, based on recent international literature and the main study's own data;
d. a budget impact analysis and, if applicable, a pharmacoeconomic model.

The National Health Care Institute expects that a period of four months will generally be sufficient for processing this information and arriving at a final advisory report or clarification and will usually have a clear answer as to whether the medicinal product will be included in the health insurance package before the end of the period of conditional inclusion. The National Health Care Institute will assess whether this is the case based on interim and clinically relevant outcome measures, as well as other package criteria. In some cases, however, four months may be too short, e.g. if the marketing authorisation holder submits an incomplete dossier. In this case, the submitting parties will have a maximum of two months to update the dossier before it can be processed. Naturally, the National Health Care Institute seeks to prevent this type of delay by informing the applicantson the dossier requirements[12] at an early stage. The final assessment may result in one of the following outcomes:
1) the medicinal product exits the conditional inclusion process and is included in the

[11] Unpublished study reports will only be considered acceptable if the marketing authorisation holder also shares all study data in a format that can easily be analysed and if the Zorginstituut is allowed to quote said data in order to draw up its final review. The research report must discuss the following in detail: the patient selection process, inclusion and exclusion criteria, the objective and design of the research, the research method, the clinical outcome parameters, the analysis method (intention to treat, non-responders), activity and side effects.
[12] (https://www.zorginstituutnederland.nl/over-ons/publicaties/publicatie/2016/08/29/instructies-voor-aanlevering-farmaceutische-dossiers)

basic health care package;
2) the medicinal product exits the conditional inclusion process and is not included in the basic health care package.

Early final review
Applicants for conditional inclusion may opt to submit a final dossier to the National Health Care Institute early, provided that the dossier contains new, published data. In addition, new circumstances, such as a new assessment framework, may give rise to an early assessment. The National Health Care Institute will determine whether these new circumstances allow for an early final assessment on a case-by-case basis. Early submissions may result in the following outcomes:
1) the medicinal product exits the conditional inclusion process and is included in the basic health care package;
2) the medicinal product exits the conditional inclusion process and is not included in the basic health care package;
(3) the conditional inclusion process is continued.

Annex 1: Dossier requirements for a conditional inclusion application

The dossier requirements are as follows:

Part 1: Background information

a. Description of the intervention.
b. Description of the registered indication and, if applicable, the specific indication within the registered indication for which the marketing authorisation holder wishes to request reimbursement in the context of the conditional inclusion process.
c. Data on quality of life (EQ-5D-5L) and life expectancy of patients with the condition without treatment with the new medicinal product.
d. Description of standard or usual care.
e. Systematic review of the available effectiveness data relating to the medicinal product in question.
f. Description of the crucial evidence gap.
g. Substantiated estimate of the expected effectiveness gains resulting from the use of the medicinal product in question.
h. A description of the position if the medicinal product in official guidelines and in treating physicians' arsenal of interventions.
i. Proposal for the implementation, de-implementation and exit strategy if the medicinal product fails to be in accordance with established medical science and medical practice.
j. Opinion of the relevant professional group(s).
k. Opinion of the relevant patient organisation(s).

Part 2: Information on feasibility

a. Letters of intent from hospitals or healthcare institutions stating their participation in the study.
b. Letter of intent from researchers stating that (part of) the care (medicinal product and follow-up) will be offered to patients locally, if possible and responsible, to maximise access to the medicinal product.
c. Letter of intent from the professional groups involved, stating that the medicinal product in question will not be offered to patients outside the study and that they will enter relevant data into the register.
d. Letter of intent from the patient association(s) involved, stating that they will support the studies (by participating in tests and filling in questionnaires).
e. Letter of intent from committee members, stating participation in the indication committee, consisting of an independent chairperson and independent experts and having an odd number of members.

Part 3A: Information on the proposed research/study

a. The research question and study protocol. The evidence gap should be identified clearly. Design, inclusion and exclusion criteria, comparative interventions, power calculations and group size, duration, follow-up, *go/no-go* moments (number and interval), (interim) outcome measures (including quality of life, such as EQ-5D-5L), statistical analysis. This could include an ongoing (international) study.
b. If applicable: information/data required for a pharmaco-economic analysis[13].
c. Information on other ongoing studies.
d. Feasibility study and timetable. If applicable: the reason(s) why the desired duration of the study exceeds the standard 7-year period.

[13] Zorginstituut. Guideline for economic evaluations in health service. (Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg.) 2016

e. Research budget.

Part 3B: Information about the proposed secondary study or register study

a. The research question and study protocol. The study should provide information on the appropriate use of the medicinal product in Dutch medical practice. The data to be collected in the secondary study should be determined in advance.
b. Plan and timetable for data analysis at the end of the conditional inclusion period.
c. Research budget.

Part 4:

a. The report of the meeting with the National Health Care Institute about relevant aspects of the medicinal product concerned (PICOt, clinical relevance of the effect, sub-groups, go/no-go criteria (objectively formulated and medically substantiated), the presence of an expertise centre, indication committee and the availability of domestic and/or international registers).