Report

Guidance for Outcomes Research

'for the assessment of the cost-effectiveness of in-patient medicines'

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Summary

NZa policy regulations In-patient medicines	In 2005, in order to improve the funding and provision of in-patient medicines, the Minister of VWS asked the NZa to alter the existing expensive medicines policy regulation and draw up a new policy regulation for orphan drugs in academic hospitals. These two NZa policy regulations came into force in 2006. The temporary inclusion of an in-patient medicine or orphan drug in one of the policy regulations results in an additional funding of 80% or 100% respectively. The NZa asks CVZ to assess the possibility of a temporary inclusion of in-patient medicines in the policy regulations (t=0). The right to this temporary additional funding is linked to the collection of data from clinical practice, i.e., outcomes research. After 4 years[1], this forms the basis for a decision on continuing the additional funding. In 2006, in order to ensure that assessments are carried out transparently and consistently, CVZ published the "Procedures for the assessment of in-patient medicines" and the "Framework for assessing the cost-effectiveness of in-patient medicines".
T=0 assessment criteria	On the basis of the file submitted by the applicant, for the t=0 assessment, CVZ examines the following criteria: the cost prognosis; the therapeutic value; and the framework for outcomes research. Advice on temporary inclusion will result if the in-patient medicine fulfils the cost criterion of a minimum of €2.5 million per year *and* it has a therapeutic added value in comparison with the standard treatment. Furthermore, there must be an elaboration of the framework for outcomes research, which means that it must contain a cost-effectiveness indication and a detailed proposal, with grounds, for outcomes research.
Question addressed by the outcomes research t=4	For the t=4 assessment, CVZ examines the following criteria:

[1] N.B.: A 3-year period was initially chosen. For pragmatic reasons this period has been extended to 4 years. In 2009 it became clear that WMG-parties generally spend a year on logistics and fund-raising before being able to start outcomes research. A 3-year period will be sufficient once the infrastructure has been established.

assessment criteria

Cost-effectiveness

Appropriate use

the cost criterion, the therapeutic value, the cost-effectiveness and appropriate use. Decision-making will be based on the actual costs involved and the question of whether including the medicine, considering its therapeutic value and cost-effectiveness, is still in the interests of public health. Insight into clinical practice, the dynamics of clinical actions, is essential to determining these criteria. Determining the appropriate use of an in-patient medicine is what enables us to get a better insight into these dynamics.

Temporary admission

Outcomes research

Crucial questions

The new aspect of this system of costing is its (in principle) temporary nature, which is linked to collecting additional data in clinical practice by means of outcomes research in the period that lies between temporary inclusion and decision-making. Its newness relates to the fact that the assessment of cost-effectiveness and appropriate use will be based on data from the outcomes research. Obviously, research on which the cost-effectiveness of in-patient medicines is based must fulfil the current 'Guidelines for pharmacoeconomic research'. The crucial questions are: 'What do we mean by outcomes research within the framework of the NZa's policy regulations?', 'Which data do we need to collect in order to be able to issue a statement on cost-effectiveness and appropriate use?' and 'How can we design outcomes research as pragmatically as possible?'

Workgroup

Goal

In 2007, in order to address these questions, CVZ set up the workgroup 'Assessing the cost-effectiveness of in-patient medicines', with experts from relevant disciplines. The aim of the workgroup is a practical, in-depth, elaboration of the framework for assessing the cost-effectiveness of in-patient medicines within the framework of the assessment procedure. The workgroup has established and elaborated upon relevant methodological aspects of outcomes research and discussed them with the parties involved during an 'invitational conference' The result of the talks and discussions can be found in this 'Guidance to outcomes research'.

Guidance
Guideline differentiation
Practical

The 'Guidance to outcomes research' is a detailed specification of the 'Guidelines for pharmacoeconomic research' and contains practical information for conducting outcomes research. It pays attention to both the different types of data

information and the desired infrastructure for carrying out outcomes research. Clearly, operationalising the NZa policy regulations involves content-related and policy-related aspects. The workgroup's focus will be on content-related aspects, the elaboration of which is described in sections 2 to 6 inclusive.

Type of data This 'Guidance' clarifies what we understand by outcomes research within the framework of the policy regulations. We conclude that determining the cost-effectiveness and appropriate use of a medicine four years after its provisional inclusion will always require data from the following categories: patient characteristics, clinical data, costs and patient-reported outcomes. The set-up of outcomes research and the nature of the data collected will be determined by the medicine (or its registered indication), the data available and the uncertainty of these data.

Possible data collections For the assessment criteria, we distinguish between three possible data collections: specific – and therefore limited – data collection, broad data collection and a minimal dataset. Establishing which data collection is required will determine how the outcomes research will be implemented. In many cases, outcomes research will be conducted using a patient registry. The data collected will eventually go into a model study in order to calculate the cost-effectiveness of the medicine. What is important here is that cost-effectiveness is not an intrinsic characteristic of a medicine. The cost-effectiveness of a medicine is always determined within the specific context of patient population, treatment strategy and comparative treatment possibilities.

Patient registry

Model study

Flow diagram The above aspects have been summarised in a flow chart as a basis for setting up outcomes research pragmatically.

Active participation of persons involved This 'Guidance' emphasises how essential it is that all persons involved actively participate in setting up and carrying out outcomes research. The requesting WMG-party is responsible for the file upon initial assessment, for realising outcomes research and for the file produced after four years. To allow this process to take place smoothly, it is important to involve all interested parties, such as the applicant, the professionals, the patient association, manufacturers, and even other people, such as health economists and other methodologists. The

Professionals

active participation of the professional group concerned is particularly essential when setting up and implementing outcomes research. The professional group should be involved even at the preliminary stage of determining the framework for outcomes research and the therein formulated proposal for outcomes research.

Pragmatic

Prospective patient registry based on indication

Infrastructure

This 'Guidance' also emphasises that the set-up of outcomes research must be pragmatic. In many cases the preferred set-up for outcomes research will be a prospective patient-registry based on the indication. Patient-registries are practical and valuable sources when collecting data on cost-effectiveness and appropriate use. These are not the only aims that make setting up patient-registries interesting. They are also valuable for revealing the dynamics of clinical actions. The data provide insight into the treatment of an indication/disorder. Physicians can optimise therapy on the basis of such feedback. The workgroup emphasises that setting up patient-registries requires a proper infrastructure.

1. Introduction

Key messages

1. Research on which the cost-effectiveness of in-patient medicines is based must comply with the 'Guidelines for pharmacoeconomic research'.
2. In principle, in-patient medicines are eligible for extra temporary funding. It is essential to obtain additional research data by means of outcomes research.
3. The 'Guidance to outcomes research' is a detailed specification of the pharmacoeconomic guidelines, and provides a pragmatic basis for setting up and carrying out research. Its aim is to be able to determine the cost-effectiveness of in-patient medicines in clinical practice. The Guidance pays particular attention to the dynamics of clinical actions and the appropriate use of in-patient medicines.
4. For a clear understanding, we use the following definitions:
   Effectiveness – cost-effectiveness of the in-patient medicine in daily practice, expressed in costs per QALY and/or costs per life-year gained, in comparison with the comparative treatment.
   Appropriate use– using the medicine in daily practice on a defined group of patients, resulting in a therapeutic value demonstrably greater than that of other treatment possibilities that are already available.
   Outcomes research - the collection, from daily clinical practice, of data that are useful for substantiating cost-effectiveness and determining the appropriate use of the in-patient medicine within the framework of the additional funding for in-patient medicines.
5. The set-up of outcomes research depends on the medicine (or the registered indication), the data available and the uncertainty of these data at the moment when the application was submitted.
6. The active participation of the professional group is essential when setting up outcomes research. The professional group should be involved even at the preliminary stage, when establishing the framework

for outcomes research and the therein formulated proposals for outcomes research.

7. Cost-effectiveness does not need to be based exclusively on Dutch data. The use of foreign data is permitted for certain cost-effectiveness data, such as clinical cost-effectiveness and utilities. Appropriate use must be based on Dutch data.
8. The party applying under the Health Care Market Organisation Act (WMG) is responsible not only for creating the file at the initial moment of submitting the application, up to inclusion in the policy regulation, but also for the actual outcomes research and the file based on which the *College voor Zorgverzekeringen* (CVZ) re-assesses the medicine after three years. It is important that all interested parties – such as the applicant, the professionals, patient associations, the manufacturer, health economists and other methodologists – are involved in compiling the file and implementing the research.
9. In an exceptional case where research cannot reasonably be carried out by the applicant or another interested party (such as the manufacturer), co-funding can be requested from ZonMw. After the medicine has been included in the policy regulation by the Dutch Healthcare Authority (NZa), the professional group or another WMG-party can apply to the ZonMw for co-funding, basing their application on the framework for cost-effectiveness that was approved by CVZ.
10. After four years, decision-making takes place over whether inclusion in the policy regulation – and, therefore, the extra funding – will continue or not. Applicable criteria are the actual costs incurred and the question of whether including the medicine, in view of its therapeutic value and cost-effectiveness, is still in the interests of public health. Insight into clinical practice – the dynamics of clinical actions – is essential when determining these criteria. Determining the appropriate use of an in-patient medicine is what enables us to charts these dynamics.
11. The effectiveness, or cost-effectiveness of the in-patient medicine is one of the criteria for decision-

making. It is essential that the incremental cost-effectiveness ratio (ICER) is properly substantiated and robust.

12. Advice and decision-making are impossible without cost-effectiveness.

1.a. Background information

Policy regulations in-patient medicines

In 2005, in order to improve the funding and provision of in-patient medicines, the Minister of VWS asked the NZa to alter the existing expensive medicines policy regulation and draw up a new policy regulation for orphan drugs in academic hospitals[1,2,3]. These policy regulations came into force on 1st January 2006. Within the framework of these NZa policy regulations, CVZ assesses, at the request of the NZa, the possibility of temporarily including expensive medicines and orphan drugs in the policy regulation concerned, thereby providing access to additional finance. For temporary inclusion, the *College voor zorgverzekeringen* (CVZ) and its Medicinal Products Reimbursement Committee (*Commissie Farmaceutische Hulp*, CFH) assess the product's cost prognosis, its therapeutic value and the framework for outcomes research. Re-assessment subsequently takes place after four years, which establishes the actual costs incurred by the medicine, assesses the therapeutic value and cost-effectiveness and provides clarity on appropriate use. On the basis of this re-assessment, the NZa decides whether to extend the medicine's inclusion in the applicable policy regulation.

Additional funding

Temporary

Link with additional data collection

A new aspect of this system of funding is its – in principle – temporary nature, which is linked to outcomes research for collecting additional data. This is in keeping with an international development, whereby policy-makers use the instrument of temporary inclusion linked to the collection of additional data[4]. This facilitates additional funding or reimbursement for promising though as yet insufficiently proven medical interventions for indication fields with limited alternative treatment possibilities. The aim is to collect data in order to reduce uncertainty regarding the value of the technology. Using temporary inclusion in this way has a number of advantages:

- patients are granted access, in a controlled setting, to a

new technology for which there is as yet insufficient evidence for its definite application;
- increased verification regarding effectiveness and cost-effectiveness;
- it provides an opportunity to promote innovative medical interventions and their further development for specific indications and patient populations.

Assessment In-patient medicines

CVZ started assessing in-patient medicines in 2006. To this end CVZ elaborated upon the assessment procedures for these medicines in the "Procedures for assessing in-patient medicines"[5]. Appendix 5 of those procedures describes the

Procedures

requirements for compiling the file. CVZ has drawn up an assessment framework for the purpose of assessing the

Framework

framework for outcomes research and the cost-effectiveness indication and for assessing, after four years, the cost-effectiveness of in-patient medicines[6]. It contains the main outline of the requirements with which the framework and the cost-effectiveness must comply.

Pragmatic

CVZ has a pragmatic approach to implementing outcomes research. The requirements laid down for the party applying under the Health Care Market Regulation Act (*Wet Marktordening Gezondheidszorg*, WMG) must be realistic, taking into consideration the interests of society, the applicant's research capacity, the availability of data and funding for the research. Outcomes research should therefore be goal-oriented. It is important to collect only data that are essential for assessing cost-effectiveness and which provide insight into the appropriate use of the medicine.

Workgroup

In order to facilitate a pragmatic interpretation of outcomes research, CVZ set up a workgroup for 'Assessment of the cost-effectiveness of in-patient medicines'. The aim of the

Aim

workgroup is an in-depth, practical elaboration of the framework for assessing the cost-effectiveness of in-patient medicines. The focus of the workgroup will be outcomes

Guidance

research. This 'Guidance to outcomes research' was drawn up as the result of the deliberations of the workgroup.

1.b. Assessment of in-patient medicines

Medicines in hospitals are funded via hospital budgets that are drawn up annually and via diagnosis treatment combinations

(DBCs). The rapidly increasing costs of in-patient medicines can lead to financial bottlenecks in hospitals, which could put pressure on access to these medicines. The aim of the policy regulations is to promote equal access for all patients to treatment with in-patient medicines. Hospitals receive extra funding for in-patient medicines that are included in the policy regulation in the form of 80% reimbursement of the costs of expensive medicines and 100% of the costs of orphan drugs. The NZa policy regulations are nothing more than a budgeting instrument. Inclusion in the policy regulation does not regulate the statutory right to medicines in hospitals. Patients have a right to medicines in accordance with that which is stated in article 2.1 of the Health Insurance Decree: 'The content and extent of the forms of care and services will be determined in part by established medical science and medical practice, and where such a standard is lacking, by whatever is equated with responsible and adequate care and services in the professional field involved'.

Application for inclusion in a policy regulation by a WMG-party

Every party that is subject to the WMG can submit an application for inclusion in the NZa policy regulation. This includes hospitals (NVZ, NFU), professional groups (Orde), health insurers (ZN) and patients (NPCF). In practice, the Dutch Association of Hospitals (NVZ) and the Dutch Federation of University Medical Centres (NFU) submit most applications for the inclusion of, respectively, in-patient medicines and orphan drugs. Though manufacturers are not officially WMG-parties, they are clearly important interested parties. It is no more than logical to involve manufacturers in the compilation of files and the implementation of research – after all, manufacturers have access to all the information that was necessary to register an in-patient medicine and stand to gain from its inclusion in the NZa policy regulation.

Fixed assessment criteria

At the request of the NZa, CVZ assesses medicines according to fixed criteria that have been elaborated upon in the 'Procedures for assessing in-patient medicines'[5]. Just as with out-patient medicines, the substantiation of the cost-effectiveness of in-patient medicines must fulfil the 'Guidelines for pharmacoeconomic research'[7]. What is new for these medicines, is that the data obtained from additional research relate to cost-effectiveness in daily practice. This is why the

Assessment of cost-effectiveness after 3 years

assessment of cost-effectiveness only takes place after three years. This is unlike the assessment of out-patient medicines, which usually takes place once only, immediately after registration, for the benefit of reimbursement via inclusion in the Medicine Reimbursement System (*Geneesmiddelenvergoedingssysteem*, GVS).

1.c. Expensive in-patient medicines and orphan drugs

What is regarded as expensive?

What do we regard as an expensive in-patient medicine? The cost criterion for temporarily including in-patient medicines in the expensive medicines policy regulation is defined as follows: 'The total costs of a medicine, at macro-level, must amount to 0.5% of the total medication costs of the care-providers referred to in this policy regulation, with the exclusion of centres for convalescence as defined in this policy regulation, also based on the Financial Statistics of Hospitals (*Prismant*, section 4621). When determining the macro-costs of medicines, the totals will not include the costs of medicines included in policy regulations for expensive medicines and orphan drugs.[2]

Operationalisation cost criterion

In practice, the cost criterion will be operationalised as follows. An in-patient medicine is expensive if it costs a minimum of 2.5 million euro per year.

Orphan drug

An orphan drug is a drug that has been granted the special status of orphan drug by the European registration authority, the EMA (European Medicines Agency). Orphan drugs are drugs intended for the diagnosis, prevention or treatment of rare disorders. In the European Union, a disease suffered by no more than 5 per 10,000 residents is rare. For the Netherlands this would mean a maximum of 8,000 patients suffering from the disease. In-patient orphan drugs generally relate to indications for which there are far fewer patients; these are referred to as 'ultra orphan drugs'.

The cost criterion for temporarily including an orphan drug in the orphan drug policy regulation for academic hospitals is defined as follows:
'Only academic hospitals can obtain retrospective funding for an orphan drug, and only if expenditure on that orphan drug was higher, based on the expected costs, than the financial

limit of 5% of the average expenditure on medicines by academic hospitals. When determining medicinal costs, the total sum does not include the costs of medicines included in the policy regulations on expensive medicines and orphan drugs.'[3]

Operationalisation cost criterion

In practice, operationalisation of the cost criterion of orphan drugs shows that the sum is 600,000 euro per year per academic hospital.

t=0 assessments as of 2006

Since 1st January 2006, CVZ's CFH has carried out an initial assessment at t=0 for 33 medicines (see appendix II for a review). Eight of these applications related to an orphan drug. Our advice to the NZa was positive for 31 of these medicines. Inclusion in the policy regulation was possible in view of the therapeutic added value, the cost prognosis and the fact that the framework for outcomes research was sufficiently worked out. In two cases the advice was negative: in one case there was no question of therapeutic added value, and in the other case the medicine did not comply with the NZa's cost criterion. As can be seen in appendix 2, one of the first assessments was for an application for temporarily including an orphan drug in the expensive medicines policy regulation. This is possible. This can be considered if treatment with the orphan drug does not take place in a single centre in the Netherlands, thereby resulting in a failure to achieve the per-hospital cost criterion laid down in the orphan drugs policy regulation[3]. 2006 was a transition period during which CVZ provided the NZa with advice on inclusion in a policy regulation on the basis of therapeutic added value and the cost prognosis. The WMG-party who submitted the application was given extra time to draw up the framework for outcomes research. Since 1st January 2007, CVZ has assessed files integrally, i.e., including the framework for outcomes research. The NZa usually receives advice within two months.

Various indications

The summary of medicines that have been assessed to date shows that they are intended for the treatment of a range of indications: various malignancies, auto-immune diseases, macula degeneration, severe allergic asthma and metabolic diseases.

1.d. Definitions of cost-effectiveness, appropriate use and outcomes research

For an unequivocal understanding, this Guidance uses the following definitions:

Effectiveness ***Effectiveness*** – cost-effectiveness of the in-patient medicine in daily practice, expressed in costs per QALY and/or in costs per life-year gained, *vis-à-vis* the comparative treatment.

Appropriate use ***Appropriate use*** – use of the medicine on a defined group of patients in daily practice, resulting in a demonstrable therapeutic value that is larger than that of currently available treatment methods. Section 5 elaborates upon the concept of appropriate use.

No generally accepted definition of outcomes research currently exists. The concept of outcomes research is broad and, depending on the situation, open to various interpretations[8]. For example, there is outcomes research of a collective provision that can be defined as evaluating the impact of a provision on its users and on society as a whole. Narrowed down to outcomes research into health care or pharmacotherapy, it means evaluating the impact of respectively health care or pharmacotherapy on patients and society.
This Guidance has adopted the broadest definition, whereby the practical elaboration is narrower, in keeping with the framework of the NZa policy regulations. The definition is as follows:

Outcomes research ***Outcomes research*** – the collection from daily clinical practice of data that can be used to substantiate cost-effectiveness and also to determine the appropriate use of an in-patient medicine within the framework of additional funding for in-patient medicines.
This definition was derived from the international definition formulated by the ISPOR Real World Task Force[9], i.e., the collection from daily practice of data that are useful for decision-making.
Outcomes research must supply data, three years after the initial assessment, for both 1) substantiating the cost-effectiveness of an in-patient medicine and 2) the appropriate use of the medicine.
Data that provide insight into cost-effectiveness relate to cost data, clinical data, patient-reported outcomes (quality of life)

and patient characteristics (see sections 3 and 4).
Data that provide insight into the appropriate use of in-patient medicines in the Netherlands include: diagnosis and other patient characteristics, medicinal dose and the clinical course (effectiveness/side effects) (see section 6).

1.e. Framework for assessing the cost-effectiveness of in-patient medicines

The assessment framework[6] indicates what is necessary for assessing the framework for outcomes research at t=0, and for assessing the cost-effectiveness at t=4. This can be summarised as follows

t=0 framework

Framework for outcomes research

The framework for outcomes research must comply with the following four points:

1. The framework for outcomes research must describe the points of departure as defined in appendix 5 to the "Procedures for assessing in-patient medicines".
2. A requirement of the framework for outcomes research is to state a cost-effectiveness indication – an estimate of the cost-effectiveness of the in-patient medicine for the registered indication.
3. The cost-effectiveness indication, where applicable, should be drawn up in accordance with the guidelines for pharmacoeconomic research.
4. The framework for outcomes research must indicate the foundation for the outcomes research and its substantiation (i.e., the data to be collected).

t=4 framework

Framework for assessing cost-effectiveness

Assessing a medicine's cost-effectiveness takes place after three years. The following requirements apply to assessing cost-effectiveness:

1. Cost-effectiveness must comply with the guidelines for pharmacoeconomic research.
2. Reporting a statement regarding cost-effectiveness must be reliable and transparent, whereby certainty regarding the statement should be at a maximum.

1.f. Pragmatic set-up for outcomes research

Only data that are useful and necessary

CVZ feels it is important that outcomes research is set up and implemented as pragmatically and efficiently as possible, preferably collecting only data that are useful and necessary. The set-up of outcomes research will depend on the medicine, or on the registered indication, the data available and the uncertainty regarding these data at the moment the application was submitted. It is essential to have insight into the dynamics of clinical actions in order to be able to determine the cost-effectiveness of an in-patient medicine after three years. A study of the appropriate use of a medicine (see section 5) is a good method for obtaining insight into the dynamics of clinical actions.

When setting up outcomes research, applicants should, where possible, anticipate expected developments in the field in order to be able to record appropriate use properly. Preferably, a minimum data-set should be collected for every medicine in order to establish efficient prescription.

In order to set up pragmatic outcomes research into cost-effectiveness, one should preferably use the following analytical framework: the use of a representative, valid t=0 model and a value of information analysis in order to determine for which parameters extra research would be useful and necessary[10,11] (see section 2).

Cost-effectiveness does not need to be based solely on Dutch data. The use of foreign data is sometimes permitted for certain cost-effectiveness data, such as clinical cost-effectiveness and utilities. Appropriate use can only be based on Dutch data (see section 6).

Although the cost-effectiveness indication at t=0 should preferably be based on a model, a description is also sufficient. Cost-effectiveness at t=4 will usually be based on a model study, into which data from various sources can be integrated. A model study is also indicated if the collection of long-term cost-effectiveness data proves impossible (see section 2).

We recommend that outcomes research is carried out via an indication-based patient-registry. This will supply not only data on empirical treatment with the medicine but also data on the comparative treatment(s). It also provides insight into the use and costs of the medicine as well as providing insight into the dynamics of clinical actions. On the basis of such feedback,

the professional group concerned can, where necessary, adjust its guidelines on clinical actions, thereby promoting effective prescriptive behaviour (see sections 4 and 6). One disadvantage is the cost aspect. We recommend setting up structural patient-registries, which will require structural budgeting (see section 5).

Orphan drug

Outcomes research for orphan drugs will focus in particular on obtaining cost-effectiveness data about using a medicine on the right patient population according to the right dose regimen: the emphasis for these medicines will be on appropriate use. In view of the small numbers of patients and the often limited data on efficacy when these medicines are registered, we recommend that a patient-registry collects data for all patients with the given indication (see section 6).

All patients

1.g. Involvement in and responsibility for file-compilation and outcomes research

The applicant WMG-party

The requesting WMG-party is responsible for the file upon initial assessment, for realising outcomes research and for the file for assessment after three years. It is important that all interested parties, including the applicant, the professional group, the patient organisation, manufacturers, and others, such as health economists and other methodologists, are involved in drawing up the file and in implementing the research. The active participation of the professional group involved is essential when designing and implementing outcomes research. The professional group should be involved even during the preliminary stages of determining the framework for outcomes research and the therein formulated proposal for outcomes research. The supervision, logistics and practical elaboration may be sourced out to, e.g., a professional contract research organisation.

Involve all interested parties

Essential to involve the professionals

1.h. Funding outcomes research

Outcomes research costs money. It is necessary to weigh up meticulously the data necessary for determining cost-effectiveness and appropriate use , including thereby the interests of the patient and the attending physician. Research must be useful, necessary and implementable from a practical

point of view.

Funding from interested parties

The obvious place to obtain contributions to the finance of outcomes research is from interested parties, such as manufacturers, government and health insurers. The Ministry of VWS has set aside a €24 million budget available up until 2014 for funding outcomes research. The ZonMw has been instructed to use this budget, in close collaboration with CVZ, to finance outcomes research and HTA-methodology within the framework of the NZa policy regulations[12].The point of departure of the ZonMw Expensive Medicines programme is that co-financing research that is part of the framework for outcomes research is only indicated if the research cannot reasonably be implemented by the applicant or another interested party, such as the manufacturer. Once CVZ has approved an application for temporary inclusion and the NZa has included it in the policy regulation, the professional group or another WMG-party can submit an application for co-funding from the ZonMw – based on the framework for outcomes research as approved by CVZ. Furthermore, the ZonMw programme also provides the possibility of (co-)finance for specific research questions, the results of which (though not included in the framework for outcomes research) are relevant to decision-making on definite inclusion in the policy regulations.

ZonMw programme

1.i. Decision-making for funding in-patient medicines

Provisional inclusion

Provisional inclusion in the policy regulation takes place via the positive advice that follows once a medicine has a therapeutic added value, it has reached the cost threshold and the framework for outcomes research has been sufficiently elaborated upon. This means that the framework for outcomes research has a cost-effectiveness indication (t=0) and a well-substantiated proposal for outcomes research.

After 4 years

Decision-making about continuing the extra funding after four years will be based on the following three criteria: therapeutic added value, the actual costs incurred and the cost-effectiveness of the medicine. In order to determine these criteria it is extremely important to have insight into clinical practice, the dynamics of clinical actions. These dynamics can be mapped out by determining the appropriate use of the

medicine (see fig. 1).

Effectiveness is one of the criteria

A medicine's effectiveness, or cost-effectiveness, is one of the criteria upon which decision-making on the extra funding will be based. It is essential that the incremental cost-effectiveness ratio (ICER) is well-substantiated and robust, which means that the uncertainty surrounding the ICER is acceptable. Decision-making without properly substantiated cost-effectiveness is impossible and the right to additional funding will cease.

It is not inconceivable that the substantiation of cost-effectiveness will carry less weight in decision-making on certain in-patient medicines. For example, in the case of in-patient orphan drugs, where appropriate use will probably carry more weight than the cost-effectiveness. It is a known fact that the incremental cost-effectiveness ratio for these medicines will be high[13]. However, this does not mean that these medicines should be excluded, *a priori*, from extra funding. A statement on the cost-effectiveness of these orphan drugs will contribute to consistent decision-making and provide an overview of where funds are going in health care. However, outcomes research for these medicines will focus in particular on obtaining cost-effectiveness data about using a medicine on the right patient population according to the right dose regimen.

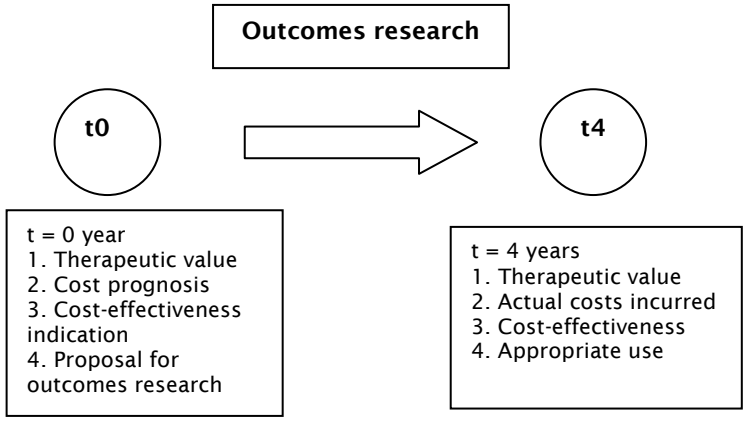

Figure 1. Assessment and decision-making criteria at t=0 and t=4.

What is cost-effectiveness?

Assuming the cost-effectiveness has been robustly and sufficiently substantiated, one can subsequently ask the question as to when a medicine is cost-effective. CVZ does not currently apply a(n) (absolute) ceiling value to cost-effectiveness. Working with a single limit lacks flexibility and does not do justice to, for example, the burden involved in the disease being treated. This means that decision-making does not require cost-effectiveness to remain under an absolute ceiling. It is imperative to have maximum possible certainty in reports on cost-effectiveness.

No absolute upper limit

1.j. Future developments in funding in-patient medicines

Funding via DBCs

Additional funding currently takes place via the NZa policy regulations. In 2010 hospital funding will shift from the present budgeting system to performance-based funding. The NZa policy regulations will probably then cease to exist, as the Minister wants the funding of in-patient medicines to take place via Diagnosis Treatment Combinations (DBCs). The costs of in-patient medicines are less suited to inclusion in the regular DBC system. This would lead to an excessive spread in the actual cost prices of the DBCs concerned, which would form a threat to an important spearhead of the DBC system –

rewards according to performance. Funding in-patient medicines may eventually take place via separate grants in the A1-segment, which will take into account the type of medicine, the indication and the dose. Altering the funding of in-patient medicines to the DBC system is not expected to have any real effect on the system for assessing these medicines. Neither will adjusting the current substitution stipulation in the NZa policy regulations have any consequences for the system of assessing these medicines.

Assessment system unaltered

Workgroup's composition, task and method of work

Workgroup

The CVZ workgroup on 'Assessing the cost-effectiveness of in-patient medicines' is comprised of experts from relevant disciplines – attending physicians, hospital pharmacists, health care academics, economists, psychologists and (pharmaco)-epidemiologists. A number of experts from the CFH also participate in the workgroup.

Aim

The aim of the workgroup is a practical, in-depth elaboration of the assessment framework for the cost-effectiveness of in-patient medicines within the framework of the assessment procedures. The workgroup has determined and elaborated upon relevant methodological aspects of outcomes research. The relevant aspects are partly based on the experience of CVZ, the WMG-parties (in particular professional groups and patients) and the manufacturers. The workgroup has also discussed international methodological discussions in the field of outcomes research.

Guidance is an elaboration of the guidelines pharmacoeconomic research

This 'Guidance to outcomes research' is the result of the deliberations of the workgroup and the discussions with the parties involved via an 'invitational conference'. The Guidance is a detailed specification of the 'Guidelines for pharmacoeconomic research' and contains practical information for carrying out outcomes research. It pays attention to both the different types of data required and the desired infrastructure for carrying out outcomes research.

Structure of the 'guidance to outcomes research' report

Subjects

During five meetings the workgroup determined and elaborated upon the following main subjects: methods of analysis, data collection and clinical practice.

The methods of analysis are discussed in section 2. They include, among other things, the usefulness of modelling

versus empirical studies. A sketch of the analytical framework is provided, with an explanation of a representative, valid t=0 model and the value of information analysis that can be used to provide statistical substantiation of parameters for which carrying out extra research would be useful and necessary. The following sections discuss the various data and parameters, as well as the sources where these can be obtained. This is about cost data (section 3), clinical data and patient characteristics (section 4), and patient-reported outcomes (section 5). Section 6 discusses clinical practice, with an explanation of situations that can arise within the framework of the dynamics of clinical actions. In order to map out the dynamics, it is essential to determine appropriate use. This can take place by determining a minimal data-set for each medicine. Furthermore, the emphasis is on indication-based patient registries, which can surmount the problems that occur in clinical practice.

Recommendations
Flow diagram
Step-by-step plan

The recommendations of the workgroup are summarised in a flow diagram that reflects the pragmatic set-up of outcomes research as well as the related step-by-step plan (section 7). The appendices include the composition of the workgroup, abbreviations used, and medicines included in the policy regulations in 2006, 2007 and 2008 (January–September).

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Part I Methods of analysis

2. Modelling versus empirical studies for the purpose of outcomes research

Key messages

1. Cost-effectiveness is not an intrinsic characteristic of a medicine, but depends on the dose schedule, the specific indication, the characteristics of the patient populations and the comparative treatment.
2. A single empirical cost-effectiveness study is seldom sufficient for decision-making.
3. With the aid of modelling, it is possible to integrate relevant data on costs and effectiveness from various sources.
4. The structure of a model must relate to the relevant patient population and reflect clinical practice accurately.
5. The data used in the model must be representative for the relevant patient population.
6. With the aid of modelling and 'value of information analysis' it is possible to determine which additional empirical data are necessary to be able to determine cost-effectiveness.

2.a. Aim

Describe the ideal structure of outcomes research within the framework of the NZa policy regulations:

- t=0: indication of cost-effectiveness on the basis of the data available, compiled in a cost-effectiveness model; 'value of information'-analysis for expressing the necessity of collecting data
- Between t=0 and t=4: collection of data
- t=4: determining cost-effectiveness on the basis of a re-analysis of the initial model

2.b. Definition and introduction

What is cost-effectiveness

There is no such thing as *the* cost-effectiveness of a medicine. The cost-effectiveness of a medicine is the impression of the cost-effectiveness of using that medicine for a specific indication, using a given dose regimen, for a specific patient population, in comparison with the usual current treatment. Cost-effectiveness can be expressed statistically: the incremental cost-effectiveness. In order to estimate this statistic, it is necessary to define the experimental treatment and the comparative treatment, whereby doing nothing can also be an option. Furthermore, it is important to determine which costs and consequences (clinical effects, patient outcome) are relevant. The guidelines for pharmacoeconomic research[1] provide pointers for the whys and wherefores of collecting certain cost data and effectiveness data and for the way in which these should be analysed and interpreted.

- Empirical cost-effectiveness study

Estimating the cost-effectiveness of a medicine can be based on an empirical, patient-based study. This involves measuring both costs and effects, on one and the same patient population, within a given period of time and comparing them to one another in an incremental cost-effectiveness ratio. This is a question of estimating the cost-effectiveness, whereby uncertainty can be determined with the aid of deterministic and stochastic sensitivity analyses. The premise of this single estimate of cost-effectiveness is that the empirical study is a proper reflection of clinical practice, both with regard to patient population and treatment, and that the study covers a sufficient period of time.

- Necessity of cost-effectiveness models

A single empirical cost-effectiveness study is, in some cases, insufficient for decision-making. Firstly, if the extrapolation of data from the empirical study is necessary in order to make a definite statement about the final cost-effectiveness of a medicine. For example, extrapolation over time if the duration of patient follow-up was too short. Another example is the extrapolation of intermediate clinical effects to outcomes relevant for the patient, such as life expectancy, whether or not compensated for quality of life. Secondly, if the empirically determined cost-effectiveness cannot be sufficiently generalised for daily clinical practice, and therefore needs to

be adjusted. In addition, when evaluating in-patient medicines, a prospective, randomised comparison of an experimental treatment versus a control treatment is often not feasible or permissible. In this case a model makes it possible to make the desired comparison 'on paper'[2]. [2]

2.c. The pros and cons of cost-effectiveness models

Countless arguments for and against cost-effectiveness models can be found in scientific literature[3,4]. The antagonists claim that models oversimplify the decision-making problem, lose the subtle distinctions of diseases and their treatment, that they create the aura of being accurate, and that models are incapable of generating new data and can be misleading. The protagonists claim that models provide more explicit definitions of (the stages of) diseases and aspects related to the treatment thereof, such as effectiveness and side effects. What is more important is that models are explicit about which data are lacking or surrounded by an excess of (statistical) uncertainty.
A fairly new argument for using models is that this is the only method that makes it possible to include all the available data and knowledge of a disorder and its treatment in decision-making. A model makes use of a multitude of data, such as cost-effectiveness of the treatment options, chances of side effects, and costs of treatment. Ideally, for all data used in the model, the most accurate estimate is made for each parameter on the basis of a systematic search of the literature and meta-analyses. On the other hand, a single empirical cost-effectiveness study will only result in a single estimate of a single parameter. By means of modelling we do not need to base our decision-making on the limited information of a single cost-effectiveness study, but can use all the 'evidence' that is available.

2.d. Modelling within the framework of the NZa policy regulations

In order to have a right to fund a medicine within the framework of the expensive medicines or orphan drugs policy

regulation in academic hospitals, a cost-effectiveness indication is required when applying for inclusion in the policy regulation (t=0). This cost-effectiveness indication can be estimated, on the basis of an empirical study, or with the aid of a cost-effectiveness model. Three years later it is possible to determine the actual cost-effectiveness. In view of the nature of the regulation, it would be impossible to do this on the basis of one prospective, randomised study. For this reason, after three years this will, by definition, involve determining cost-effectiveness on the basis of a model. The main question is, which data should be collected during these three years in order to fill this model. Which data should be collected in that specific four-year period will, of course, depend on what is or isn't known, upon initiation, about treatment with the in-patient medicine and the relevant comparative treatment (see sections H3 and H4 for the various data).

2.e. Methods

There are all sorts of models to choose from. In fact, a model is no more than a simplified reflection of reality. Within the framework of the cost-effectiveness of medical interventions, models can be regarded as a mathematic representation of the care of patients, whereby we compare data with one another that were obtained via mathematic formulas from all sorts of sources – a mathematic synthesis is created from the data available. There are two core methods for pharmacoeconomic models: decision-theory based models and Markov-models, which can also be found in combinations.

Decision-theory based models are characterised by a schematic succession of clinical events that eventually lead, via a decision-tree, to a number of final self-precluding (clinical) outcomes. The outcome of a decision-theory based model is the chance that a theoretical patient will reach one of these final outcomes, also known as the 'chance outcome'. Each separate 'chance outcome' is determined by the successive chances of all sorts of clinical events (chance nodes). An example is the chance of a serious side effect of a medicine, and subsequently, the chance of this resulting in mortality. The final outcome ensuing from this is 'deceased'. A zero-value can be allocated to such a final outcome (last node). By

giving a value of one to all the last nodes whereby a patient is still alive, we can calculate the expected result of a care strategy via the chance outcomes. By giving final nodes a continuous value (e.g., life expectation, possibly corrected for quality of life) instead of a dichotomous value, we can calculate the statistical life expectation or expected QALY. It is possible to include costs in a decision-theory based model by allocating financial values to final outcomes and/or clinical events in the model.

Markov-models differ from the decision-theory based models by incorporating the time factor. The situation of a patient is not irrevocable, but related to a time period. The Markov-model is comprised of a limited number of states of health which preclude one another (Markov-'states'). A theoretical patient can switch between these, for example, to stages of a disease or gradations of severity of the disease. We subsequently allocate a value to the Markov-'states' (life/death, quality of life, costs). Switching between 'states' is subsequently reflected, for example, in successful treatment or mortality within a given period of time. The total time that a patient 'remains' within the individual states determines the expected value of the care strategy, such as life expectation, QALY or costs.

2.f. Uncertainty and cost-effectiveness models

It is possible to extrapolate from both decision-theory based models and Markov-models on the basis of a cohort of patients or an individual patient. In the latter case, also known as micro-simulation, it is not only possible to calculate the expected value of a group of patients (as in a cohort analysis), but also the spread of this outcome (1st order Monte Carlo simulations). This is referred to as variability, or the difference between outcomes, per patient, that are determined by chance.
The most important advantage of modelling is that it provides an opportunity of explicitly coping with the uncertainty of data. There are three forms of uncertainty: the above-mentioned variability between patients, and furthermore, reliability and, lastly, heterogeneity. Reliability refers to the statistical uncertainty of model parameters. Using probabilistic

sensitivity analyses (2nd order Monte Carlo simulations) helps us to cope with this form of uncertainty. This involves simultaneously drawing 'at random' from the probability distribution of each specific parameter, and subsequently making calculations for the entire model. Doing this a thousand times creates not only a range of possible incremental cost-effectiveness values, as with conventional sensitivity analyses, but also insight into the probability distribution within that range. In this case it involves certainty about the outcome at patient population level and not at the level of the patient, as with the 1st order uncertainty or, as the case may be, variability.
Heterogeneity is the uncertainty of the cost-effectiveness that is due to differences in patient characteristics. The appropriate analysis method for determining heterogeneity is the sub-group analysis. This involves applying the model over and over, with data from specific patient groups.

2.g. 'Value of information'-analysis

A 'value of information'-analysis is a more elaborate analysis on the basis of a cost-effectiveness model. This permits us to determine what the value would be of perfect information for decision-making. After all, decision-making takes place in a situation of uncertainty – incomplete information. This allows us to calculate what the theoretical maximum budget would be in order to collect new information, in short, the research budget. The following is an explanation of the steps in a 'value of information'-analysis[6-9]. [6-9]

If the value to society of the cost-effectiveness of medical action is given a value, e.g., 20,000 euro per QALY gained, then it is possible to express cost-effectiveness in monetary terms. For example, 5 QALYs gained leads to a monetary effectiveness of 100,000 euro. If the costs of the intervention are, for example, 75,000 euro, then this leaves a net monetary benefit of 25,000 euro. Comparing interventions with one another makes it possible to calculate the incremental net monetary benefit (INMB). If it exceeds zero, then one can speak of a cost-effective intervention. If it is less than zero, then the costs of the strategy are higher than the 'benefits' and we should refrain from introducing the experimental treatment.

As indicated above, a probabilistic sensitivity analysis leads to a probability distribution of the (incremental) cost-effectiveness of a care strategy and therefore also to a probability distribution of the incremental net monetary benefit. On the basis of the average incremental net monetary benefit, it is possible to determine the choice of care strategy in relation to the comparative treatment. However, this choice is based on the imperfect information over all model parameters and could possibly be the wrong choice. In the case of imperfect information, we can calculate – partly on the basis of the marginal value of cost-effectiveness that is acceptable to society – the monetary value of a wrong choice. The chance of a wrong choice and the monetary value of a wrong choice is the value of perfect information.

The details of how this takes place are as follows: for every individual simulation in the probabilistic sensitivity analysis, we determine whether the preferred care strategy concurs with the preference on the basis of the average incremental net monetary benefit. If they are the same, the value of perfect information in the simulation is zero; in the case of a departure, the monetary value will depreciate for this simulation, whereby the incremental net monetary benefit is negative in the simulation. Calculating the average loss of value for all simulations determines the value of perfect information for a single patient. Up-scaling the value to the size of the patient population and the period during which the decision over care strategy is tenable enables one to calculate the total value of perfect information. This is the monetary value of collecting additional information, or the theoretic budget that one is allowed to spend on a study in order to obtain more accurate model parameters.

2.h. 'Value of sample information' in relation to t=0 and t=4

By repeating the 'value of information'-simulations, whereby one of a group of model parameters is always kept constant, it is possible to determine the 'value of sample information' for the model parameters concerned. Within the framework of the policy regulation, upon application for inclusion (t=0), the

'value of sampling information' could have a high value in order to determine which additional information we want to collect during the period between application (t=0) and decision-making (t=4) in order to accurately establish the cost-effectiveness of a medicine.
The results of these 'value of information'-analyses are largely dependent on the value society places on cost-effectiveness (threshold value of cost-effectiveness). As this is not fixed, varying the threshold value generates a range of results for 'value of information'.

2.i. For which problems is it impossible to update cost-effectiveness at t=0 to t=4

There are a number of situations in which it is not possible to simply update the t=0 cost-effectiveness indication at t=4, because there simply is no such thing as *the* cost-effectiveness of a medicine. Between t=0 and t=4 a shift may occur in the indication for which the medicine is used. In that case the t=0-model will not reflect the decision-making problem with sufficient accuracy. The same applies if the comparative treatment has changed or the actual nature of the experimental treatment has changed (e.g., altered dose regimen or duration of treatment). The experimental treatment may also reveal other effects or ancillary effects than the ones initially expected or established.
In these cases we would have to abandon the t=0-analysis and the resulting t=0-model and define a new cost-effectiveness model. Obviously, we would have to complete this model with data that is as accurate as possible and re-determine the uncertainty of the cost-effectiveness. Nor will the said 'value of information'-analysis at t=0 be relevant to decision-making at t=4 either, unless the t=4-moment is a correction for further evaluating the medicine's use in the new situation.

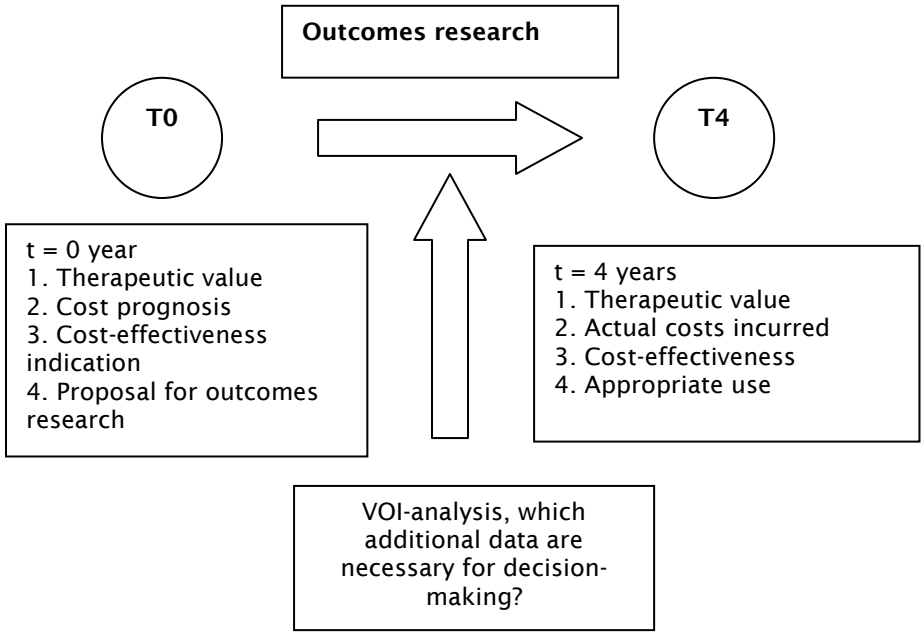

Fig. 2. Integration of the 'value of information' in the assessment at t=0 and effect on the set-up of outcomes research.

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Part II Data collection

3. Cost data

Key messages

1. The point of departure for cost research is formed by the Guidelines for pharmacoeconomic research, and the elaboration thereof in the Instructions for Cost Research.
2. The preferred choice is the societal perspective, whereby both direct medical costs and direct non-medical and indirect non-medical costs are included.
3. Costs = quantity x cost price. Measuring amounts of health care and absenteeism due to illness is usually preferred to measuring the costs these involve. Cost prices used should be a realistic reflection of the value of the means deployed, where possible making use of standard prices and *Taxe*-prices and not tariffs.
4. Preference goes out to estimating the costs for the same patients, or a representative sample thereof, as those in the outcomes research. Possible data sources are the patients themselves, their care-providers or existing registries.
5. In all cases, merely providing a report of the costs of the medicine being studied is insufficient. Relevant are the differences in costs between treatment strategies, in relation to the difference in cost-effectiveness.

Cost data form an essential aspect of outcomes research. They quantify the value to society of deploying the means that are associated with a given disorder and its treatment. The Guidelines for pharmacoeconomic research[1] and their elaboration in the Instructions for Cost Research[2] form the point of departure when identifying, measuring, valuing and analysing cost data. They are intended to promote uniformity and standardisation of pharmacoeconomic evaluations.

3.a. Perspective and cost categories

Outcomes research is usually carried out from the societal perspective. This perspective may differ from that of health

care or the perspective of specific care-providers and insurers. This will affect the choice, both in including and in valuing the specific cost categories. Meticulous substantiation is necessary when the choice falls upon some other perspective than that of society.

The usual classification of costs to society is into direct and indirect costs, both within and beyond the field of health care (table 3.2). Direct costs within health care are first and foremost the costs of the primary medicinal treatment itself. But they also include other costs relating to the prevention, diagnostics, therapy, revalidation and care of the disorder, which are central to the outcomes research. Examples of direct costs beyond the field of health care are patients' travelling costs or costs of patients' time, the costs of self-medication and those of informal care. Indirect costs within health care are the costs incurred during the life-years that the patient gained due to the treatment[3]. There is some discussion about whether this category of costs should be included[4,5]. According to the pharmacoeconomic guidelines, indirect medical costs should only be included in as far as they are related to the intervention studied. Indirect costs beyond the field of health care relate to the costs in other sectors of society, in particular the costs of loss of productivity as a result of the disorder or the treatment.

The categories of costs that are relevant will differ per study. In outcomes research, what matters in the end is the evaluation of the so-called incremental costs, i.e., the difference between the costs of a treatment strategy with the new medicine and with an alternative. These incremental costs will often have to be estimated on the basis of the total costs for the various strategies, particularly with respect to primary medicinal treatment. For some categories of costs, finding a relevant difference in costs may be so improbable that measuring this category of costs can justifiably be omitted in advance. For example, when studying in-patient medicines, it may be self-evident that a difference in cheap self-medication would never be sufficient to affect the conclusion of the evaluation. On the other hand, experience teaches that we may easily overestimate the economies that result from an effective treatment. For this reason economies in, e.g., labour

productivity, can only reliably be claimed it they have actually been measured.

3.b. Measuring and valuing

Once the relevant categories of costs have been identified, they have to be measured and valued. Although payments can be measured directly, they are not usually regarded as a valid means of assessment. After all, they do not necessarily reflect the actual costs. Instead it is often better to differentiate costs, on the one hand according to quantities, and on the other hand according to cost prices: costs = quantity x cost price. In this way we do not directly measure the costs, but the amount of care consumed, e.g., expressed in number of days admitted to a nursing home, number of G.P. consults or number of tablets of a given medicine supplied. The costs are subsequently calculated by multiplying amounts per patient by the related cost prices. Distinguishing amounts and cost prices increases the degree to which research results can be generalised. Nevertheless, the external validity of cost data can be considerably limited due to international differences in health care and economic climate.

Various sources of data (discussed below) can be used for measuring quantities. The optimal study subject can vary per study, whereby the determining factors include validity, representativeness, availability, timeliness, feasibility and costs. For the internal validity of a cost study, it is important that costs are measured in the same patients as in the outcomes research (or in a representative sample of these). However, it is sometimes necessary to depart from this, e.g., because the time horizon is too short to be able to make a full inventory of care consumed or because the data have to be collected retrospectively. In such cases, use can be made of care registries and other sources of data beyond one's own study.

The prices of medicines appear in the monthly updated G-standard or the Z-index (*Taxe*) (www.z-index.nl). The sums contained therein are the official invoice prices. Data from this source are only available at a fee. For this reason information on the costs of medicines can also be based on the

Farmacotherapeutisch Kompas (www.fk.cvz.nl). Those who compile the *Kompas* make use of the prices listed in the G-standard. The prescription line reimbursement and the VAT must be added to the medicine prices. For self-care products, it is sufficient to calculate the actual purchase price[2].
In addition, standard prices may be used for a product's cost price per unit. These are available for various types of admissions and consults, absenteeism due to illness and patients' travelling and time costs[2]. They are subject to an estimation of the realistic value of deployed means and are intended to promote the comparison of economic evaluations. If no standard prices are available, then data from the literature may be used. Another possibility is to make an inventory of current market prices, as long as it is a realistic reflection of the value of the means deployed. You will sometimes have to carry out your own cost price analysis, customised to the situation, e.g., itemised according to personnel, material, accommodation and overheads. The use of tariffs as cost-price is not generally regarded as a valid method of evaluation, because they do not necessarily reflect the actual cost-price. The use of diagnosis treatment combinations (DBCs) is expected to lead to a more realistic tariffing structure.

3.c. Data sources

The available sources of data differ particularly with respect to their comprehensiveness and the extent to which specific patients or groups of patients can be identified. Data sources that do not distinguish between patients treated with the new medicine and those treated with the alternative can only be used for estimating incremental costs. At best, these are suitable for, e.g., modelling medical costs in the long term or for economising on costs by completely preventing certain disorders. The advantages and disadvantages of various data sources are discussed in more detail below.

3.c.1. Patients

Patients are the spider in the web of all the care they receive and therefore represent a good source of information. Some categories of costs, such as self-medication, informal care and health-related expenditure, can only be measured by asking

the patient. Furthermore, patients can provide data on, e.g., absenteeism due to illness, which, though recorded elsewhere in registries, cannot easily be accessed due to privacy reasons.

The advantages of obtaining measurements from the same patients as in the outcomes research are enormous. It guarantees representativeness, thereby promoting internal validity. Furthermore, the measurement design can be customised according to the question being addressed in the study. A significant disadvantage is that the validity is limited according to the degree to which patients are able to remember events. This means that most measurements will have to be taken prospectively, so that the research period will have to be just as long as the time period covered by the analysis. Furthermore, selective response can lead to distorted results.

Diaries, questionnaires or interviews can be used when interrogating patients for the collection of cost data. It is important to make choices regarding the nature of the cost categories and the period to which they relate. The availability of standard measuring instruments is limited (for examples: see Hakkaart-van Roijen, 2002[6] and Reilly, 1993[7]) and research into the convergent validity of the various measuring instruments is limited[8,9]. For example, patients are poor at reporting on medication purchased. In general, patients remember the more salient forms of care better and for longer, but ideally the measuring period should not exceed three months. The advantage of a costing-diary is that patients can make entries directly after each event, which will reduce the memory effect. This makes diaries more reliable than retrospective questionnaires or interviews, particularly for open questions and the use of less salient forms of care and absenteeism due to illness[9]. From a logistical point of view, incorporating questionnaires into research is often easier. When costing-diaries or questionnaires are used, it is advisable to run through them with the patient at the moment they are returned.

3.c.2. Care-providers

Representativeness is guaranteed by the fact that care-

providers in pharmacies, G.P. practices and hospitals are capable of providing data about the same patients as in the outcomes research. Care-providers involved in primary care often already supply data for the study registry, which can then be supplemented with cost data.

The increasing possibilities of information systems allow data to be reproduced both retrospectively and prospectively. Accuracy and completeness depend on the degree to which these data are necessary for the primary care process. Though it is possible to collect additional data as well, the degree of their elaborateness and the motivation of those registering the data will form a limiting factor. Support during data collection can help promote motivation. Furthermore, care-providers will only be prepared to provide data on individual patients if those patients have explicitly granted their permission.

An important disadvantage of collecting data via the care-providers is that they are only aware of care in which they themselves are involved. This can make collecting data a time-consuming exercise. After all, each patient will have various care-providers. Nevertheless, collecting data via care-providers can be a feasible and reliable alternative, especially for data on primary treatment and for data less suited to reporting by patients, such as the purchase of medication.

3.c.3. Care registries

Many care registries exist in the Netherlands. The most complete review of these can be found on the website www.zorggegevens.nl. One of the most important data sources is the *GezondheidsStatistisch Bestand* (GSB) of the *Centraal Bureau voor de Statistiek* (CBS, Statistics Netherlands) which links various care registries to the *Gemeentelijke Basis Administratie* (GBA, Municipal Personal Records Database). Among other things, the GSB contains data about out-patient care and clinical care in almost all Dutch hospitals, based on the *Landelijke Medische Registration* (LMR, National Medical Registration). The aim is to add other registries to the GSB in the next few years, in the fields of both primary care and medicinal consumption. Linking it to the GBA will facilitate the selection of specific persons from the GSB, e.g., patients from

a given study population. However, this does not necessarily mean that these data can actually be obtained for this purpose. This also applies to other care registries containing data on individual, identifiable persons. The CBS and other registry-holders have strict privacy regulations. This means that, if one wants to make use of care registries in a cost-effectiveness analysis, right from the start of the project clarity must exist regarding possibilities for use.

If the possibility of obtaining and using data on a specific patient population exists, then it is crucially important to find out whether the registries actually provide the information that is necessary for the research. Well-known problems are the linking of data between sectors and the provision of detailed data. What is often wanted is a combination of data on care consumption in the various fields of health care, e.g., G.P. care, hospital care, medicinal consumption and home care. Or hospital care and nursing home care, in connection with care substitution for chronic patients. There may also be a demand for various other combinations. However, not all care registries use citizen's service numbers, which means linking is limited. The GSB is starting to link files, but a lot still needs to be done before a substantial segment of care is covered. The level of detail is also problematic. For example, the LMR (via the GSB) provides most information about hospital care, but out-patient care is not included, nor are hospital pharmacies, functional departments, radio-diagnostics and many other aspects of hospital care. In fact, the LMR is only useful for insight into operations (clinical and for out-patients) and the number of days nursed, with a number of background characteristics. Thus, even though it may be possible to track down a study population, the question is whether the data will be sufficient for an economic evaluation. It is important to know the possibilities when starting research.

If a study population cannot be tracked down, then it may be possible to work with a similar patient group. This will not be based on the data of individual patients, but the averages of groups that must be defined in more detail. Clearly this will increase the risks of distortion, white noise and interference. Such an approach would seem suited only to extremely crude research and crude cost categories, such as number of days

nursed. In that case one must plausibly demonstrate that the population from the care registry is representative of the population that is central to the economic evaluation.

3.c.4. Work registration

Examples of productivity costs are reduced attention and energy, absenteeism due to illness and disability, and the costs of recruitment and training when filling the resulting openings. Little is known about productivity loss during work and the costs of re-filling openings. This will require an inventory with primary data collection.

The CBS and the UWV have? national registries available for analysing absenteeism due to illness and disability. Absenteeism due to illness is particularly important for economic evaluations. The newest absenteeism registries of the CBS are linked with the municipal personal records database. This makes it possible to chart absenteeism due to illness for specific persons and groups. The files also provide information on specific professions on which it is possible to form an economic evaluation. Here also (strict) privacy regulations apply.

3.c.5. The costs of a disease database

The costs of illness (KVZ) database of the RIVM provides a wealth of information (www.kostenvanziekten.nl). The most recent version contains data on 2003. However, updates for 2005 and 2007 will soon be available.

Unlike care registries, the point of departure of the KVZ-database is formed by the total national health costs, which are subsequently categorised into all possible combinations of four characteristics: disease, age, gender and health care sector. Cost estimates are only available at an aggregated level, and then in the form of average costs over all patients with those specific characteristics. This makes the KVZ estimates particularly suited to long-term modelling of medical costs or cost economies due to the complete eradication of

certain disorders.

Data from the KVZ database cannot be used as they are. After all, they relate to the total health care costs on a national level. Using them in economic evaluations requires a translation to patient level, for example, according to prevalence statistics or more complicated epidemiological models. Furthermore, it is also necessary in order to prevent an overlap with cost estimates from the primary data collection. It would seem warranted to take explicitly into account the (substantially higher) costs in the last life-year[4,5]. The RIVM is busy developing a 'toolkit' as a handy method of utilising all these costs (in life-years gained and last life-years) in economic evaluations.

3.d. Analysis of costs

Distinguishable forms of economic analysis in which various treatment strategies are compared with one another are the cost-minimisation analysis, the cost-effectiveness analysis and the cost-utility analysis.

The cost-minimisation analysis (CMA) can be utilised when the effects of treatment with a new medicine are identical with those of the alternative. The CMA analyses only the incremental costs. In outcomes research, it will rarely be the case that outcomes are known in advance to be identical. Furthermore, an economic analysis is only required if therapeutic added value is being claimed for the new medicine. For this reason a MCA cannot be the appropriate form of evaluation.

A cost-effectiveness analysis (CEA) involves comparing the incremental costs with the incremental effects, possibly in the form of a cost-effectiveness ratio. The effects can be expressed as disease-specific effect parameters, such as mmHg for blood pressure, pain intensity or life-years gained. CEAs with disease-specific effect parameters are particularly suited to an economic comparison within a group of treatments for the same disease.

A cost-utility analysis (CUA) is a specific form of cost-

effectiveness analysis, whereby the effects can be expressed in quality-of-life-adjusted life-years (QALYs). Quality of life can be measured and evaluated with the aid of a utility instrument (e.g., the EuroQol). From the perspective of society, utilities should reflect the preferences of society, which may differ from the preferences of patients. Because utilities can be used for various disorders and treatments, CUAs can be used within a general economic monitoring framework.

According to the guidelines for pharmacoeconomic research, a cost-utility analysis must be carried out if the quality of life is improved by the medicine being assessed. In addition, one can also carry out a cost-effectiveness analysis. If the medicine is not expected to have an effect on quality of life, then it is sufficient to carry out a cost-effectiveness analysis. In view of the fact that it can be difficult to properly estimate the effect of an in-patient medicine at the moment an application is submitted (t=0), we recommend that a CUA is always carried out, and possibly, a CEA. In all cases, it is insufficient to provide a report of the costs of the medicine being studied.

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Tables

Table 3.1. Definitions

Costs	Value of the deployment of means that involve a certain disorder and its treatment, expressed in monetary terms
Costs to society	Costs, from the perspective of society, taking into account all actors in society, irrespective of who bears the costs.
Cost price	Cost per product unit

Table 3.2. Summary of cost categories

Direct costs external to health care	Patients' travelling time and expenses, informal care, related to health expenditure
Indirect costs within health care	Medical costs during life-years gained
Indirect costs external to health care	Costs of productivity losses, special education, legal costs

4. Patient characteristics and clinical data

Key messages

1. It is necessary to determine, per medicine, which data need to be collected. It would not be wise to work according to a general list that applies to all medicines.
2. The nature and degree of elaboration of patient characteristics and clinical data for research into a medicine will depend on the type of disorder or the underlying disease and the framework for the research.
3. Data should be collected not only on patients being treated with the new medicine, but also, for as comparison purposes, on patients being treated with the conventional treatment.
4. Data on the comparative treatment can be based on retrospective data sources (RCTs, patient files) or on prospective research (observational studies or patient registries).
5. If effectiveness data need to be collected, then these should form a clinically relevant final outcome that should preferably also reflect mortality or morbidity and be in line with the effectiveness parameters from the randomised clinical studies (RCTs).
6. Appropriate primary effect measures are: life-years, quality-adjusted life-years and, in the event of certain malignancies, progression-free or disease-free life-years.
7. Severe and frequently occurring side effects should be registered, both for the experimental and the comparative treatment.
8. It is important to report on the quality of the data from the various sources, also on their internal and external validity.

4.a. Introduction

New medicines appear on the market following registration procedures. The registration authorities establish the balance between the effectiveness and safety of the new medicine based on the data available at that moment. They decide whether making the innovation available as quickly as possible is in the interests of public health. However, the degree of

uncertainty due to the set of data being so limited may be such that responsible clinical application is not yet possible. In short, this is about a balance between 'speed versus reliability'.

Uncertainty
The fact that uncertainties still exist upon introduction onto the market is not challenged by any of the relevant parties in the field of pharmacotherapy. Important causes of uncertainty are:
- the selected patient population upon which clinical research has been carried out to date;
- the limited period of time during which research data have been collected;
- the effect parameter, which is usually not (yet) based on definite final outcomes;
- the as yet incomplete pattern of side effects;
- limited data in the field of quality of life and patient satisfaction;
- the unpublished status of many research results;
- choosing a comparative arm as control treatment that is not the standard treatment.

A new medicine that also involves particularly high costs brings added uncertainty about its cost-effectiveness.

Relative
The above-mentioned inadequacies are all relative. For example, three years of pre-registration research into a medicine that is intended for life-long use on a chronic disorder can be regarded as short. A comparable situation exists regarding the size of the patient population studied: for a rare disorder, a large proportion of the patient population available may already have been included in pre-registration research. For other disorders, large numbers of patients can only be exposed to the new medicine after market introduction.

The above means it is necessary to determine which data need to be recorded, per medicine, in order to reduce existing uncertainties; it would therefore be unwise to work according to a general list that applies to all medicines.

Reducing uncertainty
Pre-registration research, in the form of randomised clinical

studies and pharmacoeconomic research, is a good basis for an initial impression of the performance expected of a new medicine. However, the work is not finished upon market introduction as additional research will have to take place in order to reduce the above-mentioned uncertainties or even remove them entirely. This outcomes research[1] should take place in the 'real-world'-situation of daily clinical practice. In other words, the outcomes research is a supplement to the pre-registration research carried out earlier so it should, as far as possible, follow along the same lines. It is important to determine any uncertainties that exist and their significance. This discussion should take place primarily at the level of the scientific associations of specialists and patient organisations.

4.b. Comparative treatment

CVZ's *Commissie Farmaceutische hulp* (CFH, Medicinal Products Reimbursement Committee) assesses the therapeutic value of every medicine. One of the conditions for inclusion in the expensive medicines policy regulation is therapeutic added value. Therapeutic added value exists if a medicine immediately fills a lacuna in the pharmacotherapeutic armoury for patients with no further treatment prospects. A medicine may even provide the first form of pharmacotherapy for disorders previously only treatable with surgery. A new medicine also has added value if its effectiveness or safety seem better than those of currently available medicines.
A result of this added value could be that, in daily practice, attending physicians stop using the existing treatment and switch to the new medicine. However, this is certainly not always – nor immediately – the case. This would make it impossible to compare the new medicine with existing treatments in outcomes research in a 'real-world setting'. The methodological consequence of this is that we would have to compare the results of outcomes research with the results of the existing randomised clinical studies on the basis of which therapeutic added value is expected in daily practice, or otherwise on the basis of retrospective cohort research.

4.c. Patient characteristics and clinical data

The nature and degree of elaboration of patient characteristics and clinical data for medicinal research depends on the type of disorder or underlying disease and, obviously, on the framework for the research; relevant to this are alterations in the use of medicines and clinical outcome parameters, both in respect of the disorder and the patient. The primary goal should be that patient data serve as feedback information for the doctors involved who, after all, find themselves in an uncertain situation that lacks clarity. Obviously, the personal data (name, address, etc.) are important, as well as the vital status at any given moment in the follow-up period, date of death and cause of death

Classification systems are available for every disorder. Preferably, those based on the international classification of diseases (ICD). These facilitate links with specific disease registries, PHARMO, the LMR, cancer registration and even the DBC-registries, although the reliability of the latter is by no means certain.

Every disease can be classified according to pathological severity and/or degree of progression at the moment of diagnosis or during its course. Agreements or guidelines often exist for the former, though the latter will often prove to be a bottleneck in relation to the precision and uniformity of the description as it also depends on all sorts of medical efforts.

The fact that many rare disorders do not appear in the international classification of diseases (ICD) may affect the collection of data on these diseases. A European project is currently busy coding more rare diseases in the new ICD-11.

As variation in use has already been included in the framework for the research, it is important to include social-economic status and the presence of additional disorders as well. The most frequently used classification of severe co-morbidities that actually shorten survival is that of Charlson. On occasions one can also add the Karnofsky-index (‘performance status’) and the ‘body mass index’ (BMI).

4.d. Which other clinical data do we need to collect?

The results of randomised clinical studies of a medicine are described in the pharmacotherapeutic report. Central to this is the assessment of the medicine's therapeutic value. A medicine's therapeutic value involves all properties that are relevant to treatment, which together determine its place within therapy in comparison with other available and recommended treatment possibilities. The balance between a medicine's effectiveness and its side effects in comparison with those of the comparative treatment are what primarily determine a medicine's therapeutic value. When the CFH is establishing a possible therapeutic added value, an important role is played by the size of the group of patients and the severity (acute/sub-acute/chronic/mortal) of the disorder being treated. The full CFH criteria for assessing therapeutic value are: efficacy; effectiveness; side effects; experience; applicability; and ease of use[2].

Re: Efficacy
The efficacy of a medicine is an outcome parameter in most clinical studies. A medicine is effective if, when used in clinical studies, its pharmacological action results in a clinical or therapeutic effect. This is often measured according to an intermediate outcome. An intermediate outcome, such as a laboratory value or a physical characteristic, can serve to replace a final outcome (e.g., mortality). The efficacy of a medicine is usually all that has been assessed at the time that a medicine is allowed onto the market. The results of a clinical comparative study (usually phase 3) will have shown that, in addition to a pharmacological effect, the medicine also has a therapeutic effect. The medicine must fulfil this criterion in order to be included in the policy regulation.

Re: Effectiveness
Effectiveness is where a medicine is not only active, but research has shown, measured on the basis of a final outcome, that its application in daily practice results in the desired goal of the treatment. A final outcome is defined as a clinically relevant final outcome that reflects mortality or morbidity. Various outcome parameters are often available. Preference goes out to clinical outcomes that are relevant for the patient.

In addition morbidity and mortality can be combined to form a compound measure that reflects quality of life: the QALY ('quality adjusted life-years').

Re: Side effects
A side effect is a harmful and/or unintended effect that occurs when the usual dose of a medicine is used for the prevention, diagnosis or treatment of a disorder. Though all medicines have side effects, they differ with respect to the nature, severity, frequency and clinical relevance of the side effects. When comparing differences in side effects, the emphasis is on severe side effects and those with a high frequency. A side effect is severe if it is mortal, life-threatening, leads to invalidity or disability, or to hospitalisation or extending a period in hospital. An unexpected side effect is a side effect that does not appear on the official registered text for a given medicine. As our experience with a medicine increases, the risk of unexpected side effects is reduced, so statements about the safety of a medicine should always be interpreted in relation to the experience that has been obtained with them. An important advantage of research in practice is that the patient populations are usually larger than in clinical research, so that side effects that occur infrequently are more likely to surface. It is important to base the assessment of side effects on all the information available from randomised clinical and observational research.

Re: Experience
Experience with using a medicine is important because longer experience leads to more clarity about its efficacy and the risk of unexpected side effects is reduced. This means greater certainty about the therapeutic value of a medicine for the prescriber and for the patient.

Re: Applicability
Not every medicine for the treatment of a given disorder can be used on all patients with this disorder. If the inclusion and exclusion criteria of a clinical study of a medicine show that it has only been studied on a select group of patients, then in principle its application will also be limited to the same group. The first question when assessing the applicability of a specific medicine is, which properties are relevant in view of the

indication of the medicine: applicability on children and the elderly, in the event of organ function disorders, during pregnancy and lactation, and the presence of contraindications and interactions. A comparison is subsequently made, per relevant property, between the medicine being assessed and the standard treatment. In practice it will become apparent whether this results in concluding that application of the medicine is less broad, just as broad or broader than the standard treatment.

Re: Ease of use
Dose frequency, time of administration, administrative form, taste and packaging are properties that affect the ease with which patients can take medicines. Differences can exist between medicines. Ease of use can play a role in a patient's therapy compliance and as a result affect the course and the eventual effect of treatment. Differences in ease of use can be important in choosing between medicines. Advantages in ease of use should become apparent in the form of improved clinical effectiveness or fewer side effects in order to be able to speak of a therapeutic added value in comparison with the standard treatment.

Other aspects
It can sometimes be necessary to record information concerning the motives of doctors and/or patients to either continue treatment or to alter it. Treatment data should justify the possibility of combined treatment and the best supportive care that is necessary.

4.e. Effect parameters within the framework of cost-effectiveness

Although no firm definition exists for the concept of cost-effectiveness, in the actual practice of decision-making, policy-makers are referring here to answering the question of whether the additional costs of a new therapy are acceptable in relation to the therapeutic added value. Operationalisation takes place by calculating the cost-effectiveness ratio, expressed as costs per QALY.
QALYs are, quite literally, 'quality-adjusted life-years' which means they relate to two effect parameters:
- life-years gained and

- quality of life gained.

For some disorders it will be impossible to measure life-years gained because they are too far in the past, for example, with multiple sclerosis. There is also the possibility that no relationship exists between a treatment and any effect on mortality, for example, with macula degeneration. This means that the effect on quality of life is all that can be recorded and incorporated into our calculations.

In oncology there is a tendency to take progression-free survival or disease-free survival as primary effect parameter instead of overall survival. In comparison with the hard final outcome of mortality or quality of life, this is referred to as an intermediate – or soft – final outcome. Surrogate final outcomes, such as laboratory parameters, should not be allowed to play a role in calculating cost-effectiveness, unless properly validated 'bio-markers' are used.
A cost-effectiveness comparison is necessary in order to determine cost-effectiveness. When comparing a new therapy with an existing one, we need to know the cost-effectiveness of the existing therapy in daily practice. However, this is certainly not always the case, particularly when no post-registration studies have been carried out, so that often the only possibility is to compare with the cost-effectiveness that is expected on the basis of the pre-registration study. The randomised clinical research then takes on the role of comparative treatment. This will particularly be the case when determining the cost-effectiveness indication at the start (t=0). At the moment the outcomes research is carried out, it is often possible to collect prospective data on the medicine and the comparative treatment, so that the cost-effectiveness of both the in-patient medicine and the comparative treatment can be determined (see below and section H5).

4.f. What do we need to record?

As indicated above, it is not possible to work according to a detailed and generalised list as we need to determine, per medicine, which uncertainties exist and which data can reduce these uncertainties. The conclusion might even be that uncertainty cannot be reduced. This was mentioned in the paragraph on 'Reducing uncertainty'. When elaborating on research results, one will often be able to do no more than

make a comparison with data from the available clinical research or retrospective cohort studies.

4.g. Potential data sources

Possible sources of data can be classified into various types. A distinction is drawn between data from current trials, patient registries, patient files and prospectively set-up observational studies.

4.g.1. Data from current trials

The registration of a new medicine takes place on the basis of one or more randomised clinical studies. The treatment of patients in a study setting often continues even after a medicine has been registered. Studies in progress can continue, whether or not blind and randomised. New studies can also be set up in order to test specific treatment combinations. Very extensive data are often available on patients being treated in a study setting, including effectiveness, quality of life and health care consumption. The extent to which the data of these patients are directly useful in determining cost-effectiveness in daily practice depends on a number of factors. These ongoing studies will probably no longer be randomised, which could endanger the internal validity of the study. Furthermore, the study population generally does not reflect the entire patient population, and the controlled set-up – which is inherent to a study setting – fails to supply data from daily practice, which is not ideal for external validity.

4.g.2. Patient and cross-sectional registries

Patient registries provide data on a cohort of patients who have a given disorder and/or are receiving a given treatment. They follow patients prospectively, often to the date of their death. Not all patient registries are capable of following patients over a period of time. These tend to be cross-sectional registries. These registries contain data from daily practice and they are often larger and have more diverse groups of patients than randomised clinical studies. They also tend to follow patients over a longer period of time. Privacy stipulations form a hindrance to this type of study.

In view of the large number of patients and ease of use, it is tempting to use existing databases for outcomes research in daily practice. However, patients in these registries have not been randomly allocated to different treatment groups. Analysing and interpreting the results is therefore subject to the same limitations as with observational studies. Another disadvantage of registries is that they usually do not contain all relevant variables relating to aspects such as effect, quality of life and care consumption. Though this could be solved by linking various databases, this is often hampered by privacy stipulations and a lack of good link variables. Lastly, registries are often hampered by a considerable number of missing data. A detailed summary of all existing registries in the Netherlands that are linked to health care can be found on the website: www.zorggegevens.nl.

4.g.3. Patient files

Hospitals have detailed data on every patient who has been treated there. Data on e.g. demographic characteristics, co-morbidity, symptoms, diagnoses, forms of treatment and health care consumption can be collected in this way. How they are recorded will depend on a hospital's policy and who records the data. Many hospitals still work with paper patient files, while others process everything in an electronic patient file. Most hospitals also work with electronic information systems in which they record all data relating to laboratory results, microbiology, pharmacotherapy and radiology. Most G.P.s also use an electronic patient file, whether or not linked to G.P. registries.

4.g.4. Data from prospectively set-up observational studies

Within the framework of outcomes research, it is also possible to collect data from a follow-up study set up prospectively with this goal in mind. Advantages are that the study population is the real patient population and that all the necessary information can be collected. One point requiring attention is that patients have not been randomly assigned to treatment groups.

4.g.5. Additional data

The above-mentioned data sources contain a lot of information about various parameters that could be necessary for determining the cost-effectiveness of a new medicine. However, it may be the case that certain data cannot be found in any of these databases. For example, specific information about health status, health care consumption, patterns of the expenditure or treatment of patients, or even care-providers or the general public. One way of obtaining the necessary data is to carry out supplementary 'surveys' using specific questionnaires.

4.h. Consequences for practical purposes

In order to determine cost-effectiveness and appropriate use, we often compare the data of a new medicine with existing data. The two sets of data should be of the same quality.

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5. Patient-reported outcomes – quality of life

Key messages

1. In keeping with the Guidelines for pharmacoeconomic research, patient-reported outcomes are comprised of QALYs, which we evaluate and weigh up from the perspective of society. There are questionnaires that have been specifically validated with this goal in mind, such as the HUI and the EQ-5D.
2. The costs of research can be calculated because a full quality-of-life study, with special measuring instruments or methods of evaluation, is not always necessary. In certain cases the necessity of a full-quality-of-life study at t=0 can be determined via a '*value of information'*-analysis.
3. Data from the literature are often sufficient. Do bear in mind that using different methods of evaluation for quality of life within a single study (e.g., the HUI in addition to the EQ-5D) can undermine its validity.

5.a. Introduction

Patient-reported outcomes are outcomes whereby interpretation is largely in the hands of the patient. This is in contrast with regular clinical outcomes, such as blood values and physical symptoms, whereby observation and reporting are mainly in the hands of the researcher/clinician. Various types of patient-reported outcomes exist. Within the framework of outcomes research, the quality-of-life parameter is particularly important in as far as it can be used to determine 'Quality-Adjusted Life-Years' (QALYs). This section therefore pays particular attention to the question of how we can obtain sufficient valid and useful estimates of quality-of-life data.

5.b. Definition

The Food and Drug Administration (FDA) define patient-reported outcomes as follows:

A Patient-Reported Outcome Measures (PRO) is a measurement

of any aspect of a patient's health status that comes directly from the patient (i.e., without the interpretation of the patient's responses by a physician or anyone else) (Food and Drug Administration, 2006[1]).

Only a proportion of patient-reported outcomes are of primary importance to outcomes research on in-patient medicines. As described above, these are in particular evaluations of states of health in order to obtain QALYs (see guideline 3 of the Guidelines for pharmacoeconomic research)[2].

5.c. The perspective of society

In a cost-effectiveness analysis, it is important to approach costs from the perspective of society. This also applies to effects and therefore also to quality-of-life measurements (see guideline 6[2]). Although the societal perspective is preferred in cost-effectiveness analyses, patients are not entirely out of the picture. This is because quality of life is usually determined in two steps: 1) the patient completes a quality-of-life questionnaire (a typical 'patient-reported outcomes' step); 2) society validates the description that results from the quality-of-life questionnaire via a representative random check. Examples of questionnaires that have been validated using this 2-step method are the EuroQol EQ-5D and the Health Utility Index (HUI). The following is a description of these questionnaires.

5.d. 'Value of information'

t=0 is when the decision is made on how extensive the quality-of-life study needs to be in order to supply useful information for the outcomes research at t=4. There is no reason for assuming that such a 'value of information'-analysis will always point in the direction of a full quality-of-life study[3]. Therefore, the remainder of this section will also pay attention to ways for ensuring that the costs of data collection are kept to a minimum, so that the costs of collecting data remain in balance with the reduction in uncertainty.

5.e. Methods for quantifying health states

The obvious thing would be to collect information about the quality of life of patients both at t=0 and at t=4. A modest data collection at t=0 will be sufficient for the cost-effectiveness indication. The 'value of information'-analysis should indicate whether more data need to be collected. Health-economic studies are usually carried out using economic models, which is beneficial to the efficient collection of quality-of-life data. Almost all models represent patients as discrete health states over time. The number of health states is usually limited, generally no more than a dozen. This small number of health states means a considerable curtailment in the quality-of-life study: research is only required into the relevant health states. The following is a description of a number of typical study situations.

1) **Questionnaires based on evaluation**

The most classic method for measuring quality of life in outcomes research takes place via validated measuring instruments, such as the HUI-versions 2 and 3 and the EQ-5D. These instruments are specially intended for QALY-analyses with questionnaires validated via 'time trade-off' and 'standard gamble'. The guidelines for pharmacoeconomic research cite these validated questionnaires as first option. These questionnaires can be completed during a randomised or naturalistic trial, though – in principle – this is not always necessary. If good representatives of health states can be found external to the trial, then the same instruments can also be used to obtain evaluations of health states from the patients themselves. The scores of these representative patients then serve as a basis for the quality-of-life values for the above-mentioned health states in the economic model. Naturally, this makes it imperative that the patients really are representative of the health states in the model. In a situation involving outcomes research into in-patient medicines, such a cheap and effective study set-up is often a realistic possibility. After all, when using the method in practice, the researcher will be aware of which patients present the most relevant health states and be able to approach these patients with the questionnaires between t=0 and t=4.

One point of attention is the quality of life of the health state without the intervention being used. This is often difficult to measure once the intervention is being used widely during the period of the outcomes research: patients in the health state without the intervention then become rare. We therefore recommend issuing classification systems for collecting proper information about the initial state without exposure to the treatment at as early a stage as possible, for example around t=0.

Collecting data about quality of life outside the clinical study can lead to complications when the effect of the intervention on quality of life is small, though still regarded as relevant by the interviewers. In that case, the question is whether it would be better to determine the difference in quality-of-life between the two conditions under controlled circumstances, for example in a controlled (randomised) study. The '*value of information'* at t=0 can be helpful in determining whether this intensive study is necessary.

Various questionnaires can be used in QALY-analyses. The most frequently used, even in the Netherlands, are the EQ-5D, the SF-6D and HUI versions 2 and 3. The EQ-5D is the most frequently used instrument and has been used in a Dutch validation study that has been published[4]. HUI versions 2 and 3 were originally designed for use among young people and there is still a strong substantiation for using them on this population. As yet, unlike for the EQ-5D, no Dutch validation study has been published. For this we have to make use of foreign validation studies. The Guidelines for pharmacoeconomic research refer both to the HUI and the EQ-5D. An increasingly popular questionnaire is the SF-6D. This instrument was developed from the much-used generic quality-of-life questionnaire, the SF-36. The SF-36 is often used in the early stages of medicinal research. Converting SF-36-scores to SF-6D-scores can therefore contribute to efficient estimates of quality-of-life assessments for the economic model. Just as with the HUI, this will involve making use of foreign validation studies.

An advantage of using the EQ-5D is that it is the only one that

has been fully validated for use in the Netherlands. It is the instrument with most publications and it is free for non-commercial use. An often-cited disadvantage of the EQ-5D is a ceiling effect: a lack of sensitivity to variations in relatively good health states. In other words, with a relatively healthy study population it is advisable to take a critical look at the sensitivity of the EQ-5D and to consider whether the HUI and the SF-6D would not be better alternatives. Conversely, there is a floor effect with the SF-6D. This means that using the SF-6D is inappropriate for a population with a relatively poor state of health. Another disadvantage of using the SF-6D is that it has not as yet been fully developed. This means that greater expertise is required when using the SF-6D than, for example, the EQ-5D.

2) Using data from the literature

If quality-of-life data have already been described in the literature, one could consider using these data. In particular if the data come from thorough, empirical, foreign quality-of-life research, it would be wise at t = 0 to take a critical look at whether collecting Dutch data really would supply extra relevant information. At the same time it is important to realise that validation studies with the EQ-5D from various countries in Western Europe only reveal limited differences[5]. Thus, if the quality-of-life data are based on an impressive American study, the obvious thing would not be to put too much effort into collecting new, Dutch, quality-of-life data.

If rough empirical EQ-5D patient classification data are available from abroad, it is possible to weight these data again according to the Dutch tariff[4]. This is an elegant way, involving a relatively small effort, of increasing the credibility of the data for a national cost-effectiveness study.

Also, when using quality-of-life data from the literature, these do not necessarily have to come from (randomised) outcomes research. Quality-of-life data are sometimes useable from studies in which representative health states play a role. Just as when applied in cost research, the degree of representativeness and the quality of the study will determine the validity of this rapid method.

Searching the literature for high-quality of life-estimates for relevant health states takes place exactly the same as when searching for other relevant characteristics of treatment: most can be found in public sources such as PubMed. Specific internet sources are:

- The CEA registry site of Tufts New England Medical Center: provides lists with quality-of-life weights (preference weights) www.tufts-nemc.org/cearegistry/default.asp
- The site of the European Network of Health Economic Evaluation Databases: http://infodoc.inserm.fr/euronheed/Publication.nsf
- The site of HEED: Health Economic Evaluations Database http://www.ohe-heed.com/
- NHS Economic Evaluation Database (NHS EED) http://www.york.ac.uk/inst/crd/crddatabases.htm
- The site of the EuroQol group: www.euroqol.org

Useful articles are: Bell CM et al., 2001[6]; Chapman RH et al., 2000[7]; Earle CC et al., 2000[8]; and Pirragglia PA et al., 2004[9].

A pitfall when collecting data from the literature is combining different study methods for measuring quality-of-life[10]. A variety of classification instruments based on evaluation and a variety of alternative assessment methods sometimes give different results. If a model always involves relative alterations in comparison with the old or competing treatment, this will not necessarily create any major problems in practice as long as a single method or questionnaire is applied consistently in the model. This could be the case when different methods are used haphazardly (see also Guideline 6 for pharmacoeconomic research). This is why in outcomes research it is necessary to describe the consistent use of data from the literature in terms of one specific method of measurement.

3) Assessments by the general population

An alternative to research based on classifications of health states and the use of data already known from the literature is to obtain an independent 'assessment' of the health states by a panel from the general population[11]. This is a possible

solution when it is difficult to approach the patient population, the number of patients is small or when the health states with the old form of treatment no longer exist due to the new intervention being used. The advantage of this method is the rapid collection of specific quality-of-life data. The disadvantage is that a fair amount of expertise is required due to the complex interview methods, such as 'standard gamble', 'time trade-off' or 'discrete choice models'. Furthermore, guaranteeing a highly representative sample survey demands an enormous effort (see also the paragraph on costs below). We therefore recommend that this method is only used in consultation with experts.

4) Estimates by clinical experts
If no data are available whatsoever and there is no possibility of setting up such a study, clinical experts can be called upon to estimate the data, preferably together with experts in the field of quality-of-life measurements. A rapid method for obtaining these estimates is to ask the experts to range the health states on a scale that also shows other comparable health states found in the literature. The scientific credibility of this 'experts method' is smaller than the above-mentioned alternatives because the method is 'subjective' with respect to the observer. In other words, the method is limited to clinicians/researchers' personal assessments, unlike the observations of respondents who give their assessments independently of the clinicians/researchers. Nevertheless, this method can be meaningful as long as it is applied skilfully. This method is particularly useful at t=0 in order to rapidly arrive at a model for carrying out a 'value of information'-analysis. The individual replies of an expert will also give an impression of the estimator's uncertainty, which is an important aspect of the 'value of information'-analysis.

5.f. A clinical variation in the QALY: the Q-TWiST

A clinical variation for expressing the QALY as a combined measure of health is the 'quality-adjusted time without symptoms or toxicity' (Q-TWiST). The approach of this combined effect parameter is, in concept, slightly different from the QALY. The Q-TWiST was developed within clinical

oncology (and not in health economics) because of a desire to arrive at a single primary outcome parameter when both survival and quality of life are relevant.
An important distinction between the Q-TWiST approach and that of the standard QALY is the graphical presentation of both in outcomes research. With the QALY, quality of life is usually presented as an average over the entire group of patients. With the Q-TWiST, quality of life is also presented for each patient, per clinical stage, for example blind = 0.5; poor vision = 0.75 and normal vision = 1.0. This is only possible if the clinical states are clearly distinguished, whereby a patient can only be in one state at any given time. Differentiating between recognisable clinical states is a particular reason why the Q-TWiST is often more in keeping with the way in which clinicians and patients regard certain disorders and the course they take.
Another difference of the Q-TWiST in comparison with the standard QALY approach is that the time element is not determined by measuring a patient's health state at fixed moments in time, but by registering whether a patient is still in a certain clinical state. The number of patients and the time those patients remain in a given state are subsequently calculated with the help of a survival analysis (Kaplan Meier: descriptive, or non-parametric, Cox regression: function estimate, or semi-parametric). The QALYs required for the cost-effectiveness study can be calculated on the basis of the Q-TWiST by multiplying the average quality-of-life-score in each clinical state by the relevant surface under the 'survival curves' of the clinical state. When added together, the individual QALYs for the various clinical states result in the total number of QALYs for a given intervention[12,13]. The above-mentioned differences between the Q-TWiST and the QALY apply especially to 'normal effect studies'. If an economic model involves discrete, i.e., mutually exclusive, health states, the two methods merge together. This is also the reason why the Q-TWiST is often regarded as a bridge between health economics and clinical practice.

5.g. The perspective of patients

In many studies quality of life is measured with so-called descriptive quality-of-life questionnaires such as the SF-36, the QLQ-C30 and the WHOQOL. In addition to these well-known

generic lists, there are also a great many questionnaires specific to disease and domain which are capable of describing quality of life. Unlike the above-mentioned HUI and EQ-5D, the descriptive questionnaires represent the perspective of patients. This is because they do not weigh the outcomes from the perspective of society as do the HUI and the EQ-5D. Instead of weighing up from the perspective of society, the patient's score is compared with the distribution of the health states in the population. For example, a health state could score higher or lower than the average of that population. However, the value of that position to society is unclear: for example, is being less mobile than the average person in the population a social problem? And, if so, how great a problem? Descriptive quality-of-life questionnaires cannot answer this question, unlike the lists specially designed and validated with this objective in mind, such as the EQ-5D and the HUI. This is why the descriptive quality-of-life questionnaires have been given only a limited role in cost-effectiveness analyses. See also the explicit pointer in the Guidelines for pharmacoeconomic research, p. 11.

The limited role of descriptive questionnaires focuses on two matters. First, it is an efficient, standardised means for investigating the biggest obstacles facing patients. This is possible because the questionnaires generally provide a score per quality-of-life domain. Second, we can assume that the disease-specific questionnaires in particular have greater sensitivity to be able to register small side effects. One problem this involves is interpreting them within the framework for outcomes research: how to set these small side effects off in relation to the main effect? This problem immediately makes clear why descriptive quality-of-life questionnaires can only occupy a limited place in cost-effectiveness research. Third, descriptive quality-of-life questionnaires are often used as an effect parameter in effectiveness studies. However, in *cost*-effectiveness studies they are incapable of supplying primary final outcomes.

Descriptive quality-of-life questionnaires used to be ranked diametrically opposite to health-economic analyses[14]. This antagonism has diminished over the course of time, partly due to the arrival of innovative research whereby descriptive

questionnaires have been adjusted to make them suitable for QALY-research. An example is the work of health-economist John Brazier who adjusted the SF-36 (via the SF-6D which he designed) to make it suitable for QALYs. Another trend is that a growing number of disease-specific questionnaires have been adjusted to make them suitable for QALY-analyses. This can form an option when it is assumed that the effect of the treatment will not be apparent from a questionnaire (that has already been validated) such as the HUI and the EQ-5D[15]. Bear in mind, however, that the effect will quite probably be too small to justify the high costs. The Guidelines for pharmacoeconomic research do permit this option (p. 11), although it obviously requires much more expertise and research than when using instruments that have already been validated.

5.h. Costs of the research

In most cases, the costs of estimating relevant quality-of-life data for an economic model for in-patient medicines will be limited. If good foreign estimates exist, then no research is required. The costs of questionnaire studies are also generally limited as these are relatively less labour-intensive. Of course, all research costs time and funds will have to be available for carrying out the research, the logistics, setting up and maintaining a database and data processing. For quality-of-life research we will have to take into account the fact that in some cases both the SF-6D (SF-36) and HUI-versions 2 and 3 will demand a financial contribution even from non-commercial users. Non-commercial use of the EQ-5D is free-of-charge. Commercial users of the EQ-5D, e.g., manufacturers, generally have a subscription, which means that using the EQ-5D will not involve extra costs.

Carrying out an evaluation study independently demands the necessary expertise and a proper representative sample of the general population. This is why the costs of this type of study can increase rapidly. However, in some cases such a study can be carried out cheaply, e.g., by combining research.

Obviously, the cheapest of all is to collect data from the literature. As indicated above, this is sometimes sufficient, while in other cases the data from the literature give rise to new uncertainties. We should therefore weigh these low costs up against the limitation in reduced uncertainty: a typical value-of-information question that should be answered at t=0.

5.i. Medical-ethical monitoring and privacy

The collection of quality-of-life data with the aid of instruments, i.e., questionnaires, does not, in principle, require the permission of a medical-ethical committee. This is because the burden on patients is usually negligible. For example, the EQ-5D is comprised of only five questions. Such minimal affairs are not subject to the law governing Medical Scientific Research. The explanatory notes to that law explicitly states:

"Completing a questionnaire on a single occasion is generally not subject to the law." Website of the *Centrale Commissie Mensgebonden Onderzoek* (Central Committee on Human Research, www.ccmo.nl).

As the law governing Medical Scientific Research governs the competences of medical-ethical committees, control will not be necessary in such cases. Control will be required if the questionnaires are burdensome. If there is any doubt, the Central Committee on Human Research recommends asking the chairman of the local medical-ethical committee for advice. Naturally, it is in all cases important to adhere to the usual measures for protecting privacy. Where quality of life is embedded in a larger clinical study, then quality of life is usually incorporated into an examination of the entire protocol.

5.j. Report requirements

When reporting on quality-of-life data, it is important to indicate how data were obtained. If an empirical collection of data is involved, then it should be included in the file as a scientific report. When using data from the literature, it is necessary to

cite the source and to account for why the values mentioned in the literature are believed to be representative for the health states in the model. As described above, a point for attention is the homogeneity of the various measuring methods used.

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Part III Clinical practice

6. Clinical practice – dynamics of clinical action and appropriate use

Key messages

1. The dynamics of clinical action are defined as the differences between the application of a medicine on the basis of the registered indication and its actual application in clinical practice.
2. Relevant differences in this context are: non-representative patient populations; diffusion; 'channelling', lack of hard clinical final outcomes [i.e. final clinical end points]; limited therapy compliance; shifting indication; 'off-label'-use; different medicines for the same indication; continued treatment in spite of therapy failure; lack of sufficient safety data; optimistic prescribing within the framework of 'last chance medicine'; minimalist [/under-]treatment due to funding system.
3. Qualitative and quantitative insight into the relevant aspects of using a medicine – how these vary over time, and the variation between medicines for the same indications – is essential for an adequate interpretation of the results of outcomes research.
4. Outcomes research should be set up in such a way that it is possible to chart the relevant differences in the dynamics of clinical actions.
5. If various medicines are available for the same indication then these medicines must be compared in a single outcomes study. If this is impossible from a practical point of view, e.g., due to a long period of time between the registration of these medicines, then at the very least the outcome parameters should be harmonised with one another.
6. A minimal dataset must be provided for every in-patient medicine provided in order to determine cost-effectiveness and appropriate use.
7. A 'patient registry' or 'population-based registry' for a single indication focuses on recording all treatments, including no treatment, i.e., providing the best possible

supportive care. This is an elegant way of being able to determine cost-effectiveness, appropriate use and the budget impact of the in-patient medicines.

8. In addition to data on empirical treatment with a medicine, patient registries also provide data on the comparative treatment. They also provide insight into the use and costs of in-patient medicines and provide insight into the dynamics of clinical actions. One disadvantage is the cost aspect. Patient registries should be set up structurally, which also means structural funding.
9. Outcomes research for orphan drugs should comprise a patient registry. There is a great deal of variety in the natural course of many of these indications and clinical data from randomised clinical studies are often limited. For this reason it is essential to record the data of all patients with the indication concerned in patient registries. In such situations a minimal dataset is not sufficient.

6.a. Introduction

Market authorisation of a medicine after its registration takes place on the basis of a positive balance between efficacy and safety. This will preferably have been demonstrated in randomised clinical studies with hard outcome measures [i.e. final clinical endpoints]. Over the course of time administration in general practice may depart from the registered indication. This could mean that the outcomes of the new treatment differ from the advantages claimed upon registration. The first part of this section discusses a number of representative examples of these ‘dynamics in clinical action’ and possible effects on treatment outcomes. In the second part of this section we describe the possibility of gaining insight into these dynamics in clinical action by studying the appropriate use of medicines in outcomes research.

6.b. Dynamics of clinical action

The dynamics of clinical action are defined as the differences between the requirements for registering a medicine and data on its application in clinical practice. These differences are often apparent in a difference in the patient population, or in the use of a medicine or in the observed effectiveness and side

effects of a medicine. The following paragraphs discuss these phenomena in more detail.

6.b.1. Treated population in practice differs from population of the clinical study(/ies)

One of the most important examples of the dynamics of clinical action is that the patient population among whom the medicine was studied in the randomised clinical study is often not the same as the patient population treated in practice. Clinical research generally limits itself to a homogeneous, limited group of patients. These are mainly patients with a moderate/good condition, with few co-morbidities and co-medications. Furthermore, the follow-up duration of randomised clinical studies is generally limited. This results in the balance between efficacy and safety – as determined in randomised clinical research – often not being representative of that in daily clinical practice. The medicine, i.e. the innovation, is diffused among a heterogeneous patient population, as illustrated in figure 3 below.[11]

A number of factors determine an innovation's diffusion:

- relative advantage: the degree to which an innovation is regarded as better than the product it can be expected to replace;
- compatibility: the degree to which the innovation agrees with existing values, facts experienced and the requirements of potential users;
- complexity: the degree to which an innovation is regarded as difficult to use, i.e., user-unfriendly;
- test possibilities: more or free test possibilities for the target group promote acceptation of the innovation;
- visibility; the degree to which the results – i.e., possibilities – of the innovation are visible for other groups of potential users.

In addition, the following factors can specifically determine the diffusion of in-patient innovations:

- opinion of leading experts within the medical profession, government, patient organisations and health insurers;
- inclusion of the medicine in guidelines of the medical profession;
- inclusion of the medicine in the NZa expensive medicines policy regulation.

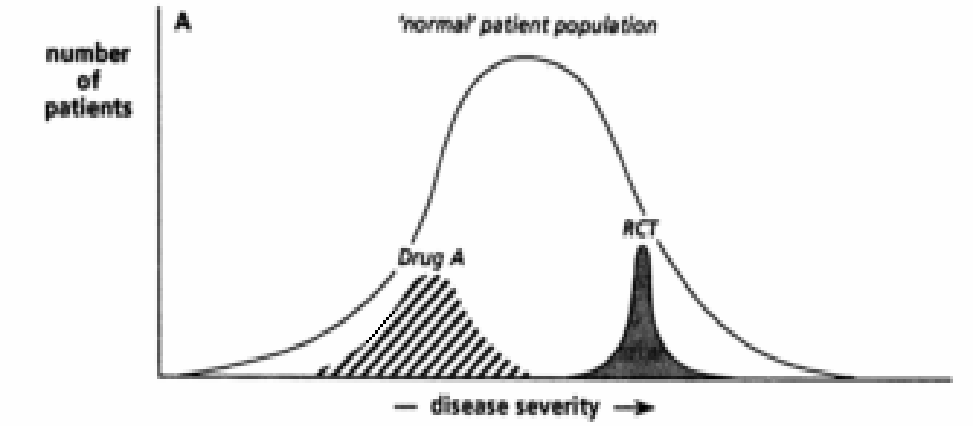

Fig. 3. Theoretical distribution of a patient population.

This figure illustrates that the patient population in which new medicine A is used in daily practice is not the same as the population that was studied for this medical disorder in the registration study (RCT = randomised controlled trial). Both situations involve the treatment of a sub-group of the total patient population.

In addition to these general diffusion processes, in clinical practice a large number of developments can lead to the patient population using a new medicine differing from the population for which that medicine was registered. These developments are:

- Insight into the optimal application of a new medicine sometimes alters even before the medicine is registered. In that case registration is always one step behind. A good example is the use of trastuzumab on patients with Her2-positive breast cancer in clinical practice before it had even been accepted into the expensive medicines policy regulation.[2] A shift from third, to second and even first-line therapy is common for oncological medicines.
- Due to selective prescribing ('channelling') patient characteristics can alter over the course of time. The prescriber often uses new medicines shortly after they are

registered for a certain group of patients who are not necessarily representative of the total group of patients who are eligible for the medicine. One reason for this is the limited amount of information available on the effectiveness and safety of the medicine in daily practice. The prescribing doctor wants to gain experience with a limited number of patients. These are often patients who do not respond well to available therapeutic options. As more positive experience about the medicine becomes available in the literature regarding the medicine's effectiveness and safety, diffusion takes place to a larger, more heterogeneous patient population.

- 'Off-label'-use. A good example is the use of bevacizumab for macula degeneration.[3] This indication is not registered, but it has turned out to be effective.
- New medicines become available for the same indication at the same time. This can lead to departure from the registered indication. Abatacept and rituximab have been included in the expensive medicines policy regulation for the treatment of patients with severe rheumatism who respond insufficiently to – or are intolerant of – other Disease-Modifying Anti-Rheumatic Drugs (DMARDs) including at least one TNF-α-inhibiting medicine. In practice, the place of these medicines, in particular in relation to one another, is subject to discussion, because there is an overlap in indication.[4]
- Critical prescription of medicines to the right patient population or subpopulation based on an interpretation of clinical research is essential. Prescribers who optimistically translate clinical research findings into practice, may not just treat patients but even harm patients, as often treatment is only effective for a defined subgroup of patients. Known examples include, in particular, out-patient medicines that do not put pressure on hospital budgets. For example, erlotinib for patients with non-small cell lung cancer who have unfavourable characteristics for a response to erlotinib, i.e., men who smoke, with a K-ras mutation in the tumour and squamous cell histology.[5]

6.b.2. Medicine's use in practice differs from use in the clinical study(/ies)

Another factor that can lead to the effectiveness of treatment in daily practice differing from its effectiveness established on the basis of the registered indication is how the medicine is used in daily clinical practice. Examples of this are:

- The dose schedule in daily practice may differ from that in the randomised clinical study. One reason could be that, in practice, in order to limit the risk of toxicity whilst retaining the same effectiveness, it proves necessary to use a medicine at a lower dose in combination with other medicines. An example of this is the use of vinorelbine for non-small cell lung carcinoma at a lower dose than that registered.[6]
- Due to the high costs of in-patient medicines, hospitals sometimes make choices on the basis of financial arguments and not solely medically-based arguments. This can lead to under-treatment: not all patients are offered the indicated therapy and/or concessions are made in the dose schedule on the basis of financial considerations.
- Therapy compliance in daily practice may be lower than that of patients in clinical studies, particularly with respect to medicines taken orally.[7] One reason could be that a patient who participates in a randomised clinical study is generally highly motivated to keep to the instructions. In addition, regular contact with study assistants and keeping an agenda reminds patients to adhere to therapy instructions properly. However, at the moment there is still a lack of clarity about the importance of therapy compliance within this group of – largely parenteral – in-patient medicines.
- Treatment with medicines may continue under certain circumstances and subsequently deviate from the advice in the registration text. An example of this is the continued treatment of breast cancer patients with trastuzumab in spite of disease progression.[8;9] Patients may still benefit from the treatment. This is often based on a small series of clinical observations and the actual usefulness of continued treatment has generally not been properly established in a good study.

6.b.3. Effectiveness and side effects in practice differ from those in clinical research

The effectiveness and side effects of treatment with a medicine in daily practice may also differ from the effectiveness and side effects that were established in randomised clinical studies. After all, there are differences in the method of determining these outcome measures. Examples are:

- The real advantage to patients of a new medicine is not always properly known, because registration often takes place on the basis of intermediate outcome parameters and not on the basis of hard clinical final outcomes [i.e. final clinical end points]. An example is the use of progression-free survival in clinical studies for determining the effectiveness of new oncolytics. We are often unable to measure overall survival because the clinical studies were too short to be able to collect the right data on overall survival. An example of this is the treatment of metastatic breast cancer with a combination of bevacizumab and paclitaxel. Though it is true that clinical research shows that treatment with this combination – in comparison with taxan monotherapy – leads to an increase in progression-free survival of patients who could not be treated with chemotherapy involving anthracycline, there is still no clarity regarding the overall survival gains to which this treatment will lead.[10]
- Side effects in daily practice can also differ from those reported in clinical studies. Such clinical studies usually have insufficient 'power' or the duration of the follow-up is too short to register (rare) side effects. Possible side effects are only brought to light during large-scale administration to patients on a daily basis. A good example is rituximab. Recently reported were two cases of progressive multifocal leukoencephalopathy following treatment with rituximab. In addition there was another case observed in a patient with vasculitis who was being treated with rituximab (www.cbg-meb.nl).

6.c. Appropriate use

The previous paragraph provided insight into the importance of the dynamics of clinical action for determining the cost-

effectiveness of a medicine at t=4 years. A good method for obtaining insight into the dynamics of clinical action is to study the appropriate use of expensive medicines. Appropriate use is defined as:

One can speak of appropriate use if the use of a medicine on a defined group of patients can be shown to have a therapeutic value greater than that of the treatment possibilities already available.

Outcomes research should therefore focus on determining appropriate use and obtaining the data necessary for determining cost-effectiveness. Below is a summary of the data necessary for determining appropriate use This is a minimal dataset that we should collect for every medicine that is prescribed. Afterwards we discuss the way in which data can be collected. The methods described are not exclusively aimed at obtaining data on appropriate use, but can also be used to obtain the data necessary for determining cost-effectiveness.

6.c.1. Minimal dataset

From an academic perspective, the obvious thing would be to collect extensive data in outcomes research because this provides an opportunity to carry out in-depth scientific research. From a pragmatic point of view it is in the interest of both patients and their doctors to collect only those data that are necessary in order to determine incremental cost-effectiveness and appropriate use.
When setting up outcomes research it is important where possible to anticipate the developments expected in practice in order to record appropriate use properly. In order to establish which data need to be collected for cost-effectiveness, it is possible, using a good t=0 model and a 'value of information' analysis (see section 2), to determine which data are important in order to determine incremental cost-effectiveness after four years.
Determining appropriate use requires a meticulous analysis of the expected use of a new medicine. The minimal dataset should contain the following data:

- Within this framework, relevant patient characteristics include:

    - socio-demographic characteristics (age, gender);
    - co-morbidity and pregnancy;
    - organ function, cognitive status;
    - therapy compliance;
    - reason for use (insufficient efficacy, unacceptable side effect, combination of various medicines);
    - medicinal anamnesis for the indication concerned
- Relevant medicinal characteristics within this framework include:
    - (maximum) dose and titration schedule;
    - exclusion of possible interacting co-medication;
- It is necessary to register the efficacy and the side effects of the treatment. With respect to efficacy, this will usually mean collecting data on clinical effect parameters, such as progression-free survival (for oncolytics) or the Disease Activity Score28 (for products for the treatment of rheumatism). It will sometimes be impossible to collect data on overall survival that are sufficiently reliable within the four year period. This applies in particular to chronic disorders, including a growing number of oncological disorders.

In addition other data can also be extremely important in order to be able to determine incremental cost-effectiveness. However, in most cases it will probably not be possible, or even necessary, to collect these in the minimal dataset.

- Quality-of-life data (see section 5). In order to be able to determine incremental cost utility after four years, it will also be necessary to measure quality of life. This can take place within a patient registry, but also in other ways, where, from a practical or methodological point of view, it is neither possible nor desirable to have this done from within the patient registry. This will require determining at t=0, per medicine, how these data are to be collected.
- Cost data will also be necessary in order to be able to determine incremental cost utility after four years. Analogous to collecting quality-of-life data, it is important to determine the degree to which these data can be collected within the patient registry or in a different way. For these data also, it will be necessary to determine at t=0, per medicine, how these data will be collected.

Lastly, in some cases it will also be important to record additional information. For example, data on the indication, its

substantiation in guidelines and the literature and the role of the prescriber (opinion-leader, academic, top-clinical) when the medicine is used in daily practice. For obtaining data required for the minimal dataset, it is essential to have access to the necessary infrastructure.

6.d. Data collection

This paragraph describes the most relevant methods for collecting data within outcomes research. Attention is given to the collection of data both for appropriate use and for cost-effectiveness.

6.d.1. Patient registry

The best way to collect data is within a patient registry' (or 'population based registry') that is set up for recording all treatments, including non-treatment, i.e., giving the best supportive care. In addition to data on empirical treatment with a medicine, using a patient registry also provides data on the comparative treatment. It provides insight into the use and costs of a medicine and insight into the dynamics of clinical action. In addition, a patient registry can make a real contribution to improving the quality of care.
A registry should preferably be based on a disorder whereby data are collected from all patients with a given disorder or group of disorders. It is important that the set-up of such a disease-specific registry is not too limited, so that one can, for example, reveal switches in oncolytic therapy from third to second and first-line therapy. An alternative is to assume a registry based on the medicine, whereby data are only collected from patients who are being treated with a single (group of) medicine(s). A disadvantage of such a registry is that it is not always possible to compare with other treatments and to reveal switches in therapies.
The use of existing data[bases] is preferred, though these will only be available to a limited degree. The point of departure could be that one always starts with an inventory of existing data collections surrounding a given disorder. Examples are:

- The DREAM-database which contains all rheumatoid patients who initially started treatment with anti TNF-α-

inhibiting medicine in 11 Dutch centres[11];
- The national cancer registry (www.ikcnet.nl), with data on cancer patients throughout the Netherlands[12];
- Lareb (www.lareb.nl). The national registry of side effects of medicines.[13] The nature of the side effects of biotechnological medicines varies greatly from those of the traditional 'small molecules'. Furthermore, the question is whether a spontaneous reporting system such as Lareb is sufficiently sensitive and capable of picking up specific safety signals or whether a follow-up study with intensive safety monitoring is more suited. Another aspect is under-reporting side effects, lack of structure when reporting, but this depends on the willingness of the doctor to lodge a report. The number of spontaneous reports in our country is high in comparison with surrounding countries;
- General medicinal databases that also collect in-patient data (or are planning to do so), such as the SFK-database (www.sfk.nl) and the PHARMO-database (www.pharmo.nl). A hospital pharmacy can also form a port of access to the cohort of patients, making use of the data on medicines provided. This route makes it possible to obtain an idea of the diffusion of a medicine to other indications than that for which it is registered.

However, these databases are almost never complete enough to be able to provide all the data necessary for collecting the minimal dataset. This means that it will be necessary to collect additional data on use of the medicine and clinical and economic outcome data. A good example of a patient registry in which existing data are linked to additional data is the new patient registry for patients with three important haematological diseases. These are for non-Hodgkin lymphoma (NHL), chronic lymphocytic leukaemia (CLL) and multiple myeloma (MM). The initial data of these patients are collected on the basis of national cancer registration. This is followed by a status study, but also by a prospective follow-up study in order to collect additional data. This takes place via collaboration between, among others, the Erasmus Medical Centre, IKZ [Integral Cancer Centre], HOVON [Dutch Haemato-oncology Foundation for Adults] and the VUMC [VU University Amsterdam Medical Centre]. A patient registry also provides

the opportunity of simultaneously comparing new medicines for the same indication in a single outcome study. For example, the DREAM-database can be used to study the cost-effectiveness and appropriate use of two new products, abatacept and rituximab. This involves patients with severe or moderate rheumatoid arthritis who have failed to respond on at least one occasion to an anti-TNF-α-inhibiting medicine. Such a patient registry also provides the opportunity of harmonising various studies with one another if there is a long time period between the registration of new medicines, for example, by using comparable outcome measures.

The obvious thing would be to use the patient registry to follow all patients from daily practice who are receiving the new in-patient medicine prospectively. Depending on the type of medicine, the disorder, the prescriptive behaviour and the data available, there are various methods for collecting data on patients undergoing the comparative treatment. This group of patients will have to be compared with the patient group being treated, irrespective of the fact that this group is not taking the new medicine.

In first instance, preference goes out to a fully prospective set-up for the patient registry. In this case the follow-up period for both groups of patients starts at the initiation of the study, as soon as the new medicine has been placed on the in-patient medicines policy regulation. It will often be difficult to create two comparable groups of patients. Selection bias may occur because doctors determine whether patients will receive the new treatment or not on the basis of the characteristics of patients. In a fully prospective study this bias can only be corrected if the new treatment is not contemplated for all patients, so that sufficient comparable patients remain for the control group. This might be the case, for example, if some doctors switch to the new treatment, while others do not. However, there is also the possibility that other differences exist between the treatments of both types of doctors, which can also lead to a distortion in the results.

An alternative can be to collect data on the use of the comparative treatment retrospectively, for example, via a status study. A problem with this type of analysis is that the

data of these patients cannot be directly compared with the prospective data of those treated with the medicine being studied. Firstly, the data from the status study are often incomplete. Secondly, over time there may be alterations in, for example the rest of the treatment, so that patients can no longer be directly compared over time. This distortion can be avoided by making use of various statistical techniques. For example, stratification, 'matching', 'propensity score matching', 'inverse probability of treatment weighting' or multivariate regression. One requirement, however, is that proper insight exists into these distortional factors. Correction for unknown factors is, by definition, impossible.

A practical solution to the problems surrounding the comparative treatment is setting up 'natural course' or 'natural history' studies that follow a disorder in a specific patient population even before the introduction of a medicine. Then, when this medicine is introduced, it is possible to use the data from these historic cohorts as controls. Such a historic study is often used in the field of rare diseases, such as Pompe's disease.[14]

6.d.2. Naturalistic or pragmatic randomised study

An alternative to a patient registry is the naturalistic or pragmatic randomised study. This involves randomisation taking place between both treatment options, without a controlled setting after randomisation. This results in a practice-based registry with the associated dynamics, with the same point of departure for each patient. There are various reasons why this option may be hampered. For example, there may be an implicit preference for one of the two treatment options. It may also be unethical to compare it with the old standard treatment, in view of the expected advantage of the new medicine. Furthermore, such a study is, by definition, temporary. At the moment that a new intervention appears to be more effective or have fewer side effects, most centres will opt for this and the study will be terminated. An example is research into the (cost)-effectiveness of palliative methods of treatment for patients with oesophageal cancer in seven hospitals in Great Britain. This involved the prior randomisation of the patients over a number of treatment

options and these were subsequently followed over the course of time.[15]

6.d.3. Randomised clinical research

For the treatment of some disorders, for example in haemato-oncology, the administration of new medicines takes place in a properly controlled study environment, even after the termination of the official clinical study. In such an environment it is possible to continue subjecting the use and the effectiveness of these medicines to controlled study. This means that randomised clinical research can be deployed in order to study the further effectiveness of the new medicines. Such knowledge can make a significant contribution to optimising therapy. For example, with respect to dose comparisons, combinations with other medicines, selection of high-risk patients and broadening or narrowing the indication. Data from such a study set-up can also be used to determine incremental cost-effectiveness. An example of such randomised clinical research is the HOVON 68 CLL[16] trial. The subject of this study was the extent to which alemtuzumab, in addition to the registered tertiary treatment of chronic lymphocytic leukaemia (CLL), could also be used in primary care in combination with cyclophosphamide and fludarabin. An advantage is that such a good highly-controlled study environment does not (as yet) exist for a large number of in-patient medicines. Setting up a patient registry would seem more realistic in such cases.

6.e. Precision, external validity and bias

It is important to take precision and the external validity of the study into account for each of the data collection methods described.
The precision or accuracy of a study can be defined as the degree to which the study shows the same results when it is repeated, i.e., whether they are reproducible. Precision is affected by the size of the study population, the size of measuring errors and the degree of natural variation in a population.

External validity stands for the degree to which the results can

be generalised, the degree to which the study results can be applied to people who do not belong to the study population. This degree of generalisability can often be obtained, but not fully guaranteed, by taking a representative random check.

Internal validity is the degree to which the effect measured – not counting chance errors – is the same as the actual effect on persons with the same characteristics as those of the study population. In other words, in order to demonstrate the effect of a medicine, it must actually be the effect of the medicine that is measured and not of another intervention or factor. Internal validity is affected by distortion, also referred to as bias. The many forms of bias can be divided roughly into three classes: selection bias, information/misclassification bias and 'confounding' bias. One speaks of selection bias when the results are distorted by an essential difference in persons in the study arm and those in the control arm. For example, during the inclusion of patients in a study, the systematic selection of patients in whom the medicine being studied has a greater effect (see 5.4.1). Information bias is the result of incomparable measurements of parameters between the groups being compared. This results in a measurement error. One speaks of 'confounding' if a causal relationship is erroneously assumed between the new medicine and the outcome, as the outcome has been affected by a third factor that is related to treatment. This could happen, for example, if it is not the new medicine itself that is responsible for an improved patient outcome, but the extra care that the new treatment involves[17].

6.f. Applicability in relation to in-patient orphan drugs

There is a large variation in the natural course of many orphan diseases and often only limited clinical data are available from the randomised clinical studies. For this reason it is essential that patient registries record the data of all patients with the indication concerned. In such a situation, a minimal dataset will often not be sufficient. Outcomes research on in-patient orphan drugs will therefore focus in particular on obtaining data about cost-effectiveness. This also applies to the various patient sub-groups and to the treatment schedule, such as clear definitions of start and stop criteria. Determining

appropriate use supplies crucial information for orphan drugs.

6.g. Requirements in relation to reporting on appropriate use

The following aspects are important when reporting on the appropriate use of new medicines:

- research into the characteristics of patients and medicines in registration studies and those in daily practice. A clear description of any discrepancies is necessary;
- research into the appropriate use of the medicine based on existing data collected as well as 'ad-hoc' data on effectiveness, safety and costs and quality of life;
- clear description of methods and an evaluation of their limitations;
- conclusions and recommendations.

6.h. Conclusions

The dynamics of clinical action are exceedingly important for outcomes research into new in-patient medicines. Prior to setting up outcomes research, it is useful first to study which facets of the dynamics of clinical action are relevant to a medicine. The next task for researchers is to take this into account in setting up that part of the outcomes research over efficient prescription. The purpose of this section – as well as other sections – is to provide useful suggestions about this. Furthermore, a proper infrastructure for outcomes research is essential.

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Part IV Elaboration

7. Pragmatic approach to outcomes research

Key messages

1. Outcomes research is necessary for every medicine that has been temporarily included in the NZa policy regulation, for determining appropriate use, and in most cases also for establishing cost-effectiveness.
2. For purposes of clarity, we make use of the following definitions:
   Broad data collection - all possible relevant data that bear a relationship to the following types of data: costs, clinical data, patient characteristics and patient-reported outcomes for the medicine and the comparative treatment.
   Specific data collection – a limited number of types of data for the medicine and the comparative treatment. It is the outcomes of the 'value of information'-analysis on the basis of the t=0 model that determine the choice of data to be collected.
   Minimal dataset – a number of standard data for the medicine that relate to patient characteristics, medicinal characteristics, effectiveness and side effects. In addition, this includes a number of data that depend on the indication.
3. ***Cost-effectiveness***

a) The dynamics of clinical action and the presence of a representative t=0 model and a 'value of information'-analysis determine the setup of the outcomes research.
b) The data collected in outcomes research can be broad or specific. In general, specific, i.e., limited, data collections are only possible on the basis of a 'value of information'-analysis.
c) Most medicines will involve dynamics in clinical action and a broad data collection will be necessary.
d) A broad data collection will often be based on a prospective patient registry based on the indication. If randomisation of patients over treatment with the medicine or the comparative treatment is neither possible nor practically feasible, then another option is post-

registration randomised clinical research.

e) Different data sources can complement one another. This applies both to broadly based and specific data collections.
f) The use of international (literature) data is possible if they are representative and usable for the Netherlands.
g) Cost-effectiveness should, ideally, be based on a t=4 model study.

4. Appropriate use

a) The minimal dataset necessary for determining appropriate use is partly fixed and partly dependent on the indication.
b) The minimal dataset relates only to data for the medicine and is comprised of Dutch data.
c) The minimal dataset should preferably be collected in a prospective patient registry based on the indication. If the data collection for determining cost-effectiveness is also based on a Dutch patient registry, then this registry must be used.
d) Appropriate use of the medicine supplies information about the dynamics of clinical action.

5. Costs are involved in carrying out outcomes research. An infrastructure should be provided right from the start.

7.a. Introduction

The previous sections have provided clarity about our definition of outcomes research within the framework of the policy regulations. Three years after provisional admission, in order to determine the cost-effectiveness and appropriate use of a medicine, data will always be needed from the following categories: patient characteristics, clinical data, costs and patient-reported outcomes. The medicine, or the registered indication, the available data and uncertainty regarding these data will determine how outcomes research will be set up and will determine the nature of the data collection.
This 'Guidance for outcomes research' distinguishes, for the purpose of these assessment criteria, between three possible data collections: a specific – and therefore limited – data collection, a broader data collection and a minimal dataset. Establishing the data collection required determines the way in which the outcomes research will be implemented. In many

cases outcomes research will take place by means of a patient registry. The data collected will eventually be incorporated in a model study for the purpose of calculating the cost-effectiveness of the medicine. It is important here that the cost-effectiveness is not an intrinsic characteristic of a medicine. The cost-effectiveness of the medicine is always established within a specific context of patient population, treatment strategy and comparative methods of treatment.

Cost-effectiveness is not an intrinsic characteristic of a medicine, depending on the context

7.b. Flow diagram as an aid to setting up outcomes research pragmatically

The flow diagram in Figure 4 unites the four aspects that are described in this 'Guidance for outcomes research'. The aim of the flow diagram is to make it clear, in a provisional registration situation, which data collection is suited to a specific situation and how the outcomes research should be carried out. The flow diagram, though non-directive, is an attempt to provide a basic tool for the pragmatic implementation of outcomes.

Composition of the flow diagram

Obviously, it would be impossible to incorporate into the flow diagram all possibilities that could occur in practice, which is the reason for this short explanation. The flow diagram consists of two elements. The upper section, part I, relates to elaborating upon the study for the purpose of determining the medicine's cost-effectiveness. The lower section, part II, relates to the elaboration for determining the appropriate use of the medicine. Both have been incorporated into the same flow diagram in order to emphasise the relationship between cost-effectiveness and appropriate use. After all, insight into the appropriate use of a medicine provides us with a picture of the dynamics of clinical actions, which is important for determining cost-effectiveness. The dynamics of clinical actions show, among other things, the actual application of a medicine and which comparative treatments are relevant for determining the cost-effectiveness of a medicine.

Cost-effectiveness

Appropriate use

Time periods

Three time periods can be distinguished in the flow diagram:

1) t=0: the moment of submitting an application for inclusion of a medicine in the policy regulation. An assessment is made of the therapeutic value, the cost prognosis and the framework for outcomes research. 2) The period of the outcomes research between t=0 and t=3, which can cover about 3.5 years. 3) t=4: the moment of re-evaluating the therapeutic value and the actual costs incurred, and assessing the cost-effectiveness and appropriate use

7.c. Defining broad and specific data collection and the minimal dataset

Broad data collection
Specific data collection

In order to set up outcomes research it is crucial to make clear what we understand by a broad data collection, a specific data collection and a minimal dataset.

The collection of broad *and* specific data is necessary for determining cost-effectiveness. A broad data collection will collect all possible relevant data relating to the following types of data: costs, clinical data, patient characteristics and patient-reported outcomes for the medicine and the comparative treatment.

Medicine and comparative treatment

A specific data collection involves a limited number of types of data for the medicine and the comparative treatment. The outcomes of the 'value of information'-analysis on the basis of the t=0 model will generally determine the choice of data to be collected. In both cases it is possible to make use of various sources of data. International (literature) data can also be used if they are representative for the Netherlands.

Minimal dataset

The minimal dataset is used for determining appropriate use(see 5.3.1). The minimal dataset is partly fixed and depends in part on the indication. The minimal dataset contains a number of standard data that are necessary for every medicine and that relate to patient characteristics,

Medicine

medicinal characteristics, effectiveness and side effects. In addition, it may be necessary to collect other data, such as quality of life data (see also 5.3.1). The minimal dataset relates

Dutch data

only to data for the medicine and is comprised of Dutch data.

7.d. Interpreting part I of the flow diagram: determining the medicine's cost-effectiveness and the step-by-step plan

Initial assessment at t=0

t=0 model study

- The framework for outcomes research must be available at t=0. This framework should provide a cost-effectiveness indication , preferably based on a t=0 model, and contain a proposal for the set-up for outcomes research.
- The WMG-party making the application has involved all interested parties in drawing up the application and the framework for outcomes research.
- In consultation with the professional group involved, an estimation of the potential dynamics in clinical action is made for the registered indication of the medicine.
- The WMG-party makes a choice for submitting a cost-effectiveness indication, which may be via a description or via a t=0 model study.
- A t=0 model study is preferred because it can be used as basis for the t=4 model. The usefulness of the t=0 model will depend on the degree of representativeness for the Dutch situation and the potential dynamics in clinical action.
- If the cost-effectiveness indication is not based on a t=0 model, then the outcomes research will require a broad data collection, irrespective of the potential dynamics in clinical action.
- If the WMG-party has submitted the cost-effectiveness indication via a representative t=0 model, then this model can be used to carry out a 'value of information'-analysis. The results of such an analysis indicate which parameters have an impact on the uncertainty relating to the cost-effectiveness indication. The outcomes research will subsequently focus on these parameters.

When does VOI make sense?

- The WMG-party should realise that a 'value of information'-analysis only makes sense 1) if there are little or no dynamics in the clinical action for the indication concerned, and 2) if the analysis is based on a representative t=0 model of sufficient quality.
- In all cases in which the professional group has estimated that dynamics are involved in a clinical action, it would be wise to draw up a representative t=0 model; this model will form the basis for the t=4 model. In this case, it would

not be wise to carry out a 'value of information'-analysis. Due to the limitations of such an analysis, the outcomes would not be of any use for defining a specific data collection and a limited data collection. In these cases, the outcomes research will involve a broad data collection.

The period of outcomes research between t=0 and t=4

- The proposal for the set-up of the outcomes research should be included in the t=0 file, as an integral part of the framework for outcomes research.
- We always determine the cost-effectiveness of a medicine in relation to the comparative treatment.
- The WMG-party should take into account that in most cases it is necessary to collect data for the comparative treatment as well as for the medicine.

Is randomisation possible and practical?

- An important question that the WMG-party should be asking is whether the randomisation of patients to the medicine and the comparative treatment is possible and practically feasible in daily practice. The WMG-party should also indicate the degree to which the lack of randomisation could affect the results of the study and the degree to which this can be compensated.

  In the case of a broad data collection, the data will largely be obtainable from a prospective registry based on the indication. In a number of cases the choice will be post-registration randomised clinical research. These possibilities are indicated in the flow diagram. Choosing a prospective patient registry based on the indication or a post-registration randomised clinical research for the medicine should take place in consultation with the professional group concerned.

- If it would be ethically irresponsible to deny patients access to the medicine, then a randomised study set-up is not an option. This is the case if the medicine is the only effective treatment for an indication, or if the clinical effect of the medicine is significantly better in comparison with existing treatments. In these cases data will be collected via a prospective patient registry based on the indication. It will often be possible to collect data for the comparative treatment from retrospective data sources, such as patient

files, or from a patient registry that already exists. See the flow diagram: question: randomisation possible?, outcome: *no.*

- If the clinical effect of a medicine in comparison with existing treatment has not become sufficiently apparent from the clinical registration studies, then in practice not all patients will be treated with the medicine and a randomised study set-up will be possible.
- Although randomisation is possible, in practice it will not always be desirable or practically feasible. This might be the case if various in-patient medicines are available for the treatment of the same indication and the professional group has not indicated a preference for treatment with the medicine or one of the other products. This may be the case, for example, if people assume therapeutic equivalence. In these cases, it is desirable to collect data for the medicine in a prospective patient registry based on the indication. Data are collected simultaneously on the alternative treatment. See flow diagram: question: randomisation possible?, outcome: *yes(1)*).
- If randomisation is possible, then in a number of cases the professional group will prefer to randomise patients to the medicine or the comparative treatment and post-registration randomised clinical research will be initiated. Combination treatments will often be the reason for setting up such research. It is easier to set up post-registration randomised clinical research for some indication fields than for others. Favourable circumstances are if the professional group sees the importance of carrying out post-registration studies and if there is a proper infrastructure for carrying out such studies. In that case, preference is more likely to go out to post-registration randomised clinical research than to a patient registry. See flow diagram: question: randomisation possible?, outcome: *yes(2)*).

Patient registry and post-registration clinical research complement one another

A prospective patient registry based on the indication and post-registration randomised clinical research complement one another. The choice will probably be for one or the other, or even both, depending on practical feasibility. Both data sources give rise to data that provide insight into the dynamics of clinical action and data that are

useful for determining cost-effectiveness. The interaction and the relationship between these data sources is emphasised in the flow diagram, via an interaction arrow and the box.
As indicated above, an existing patient registry also makes it possible to obtain data on the comparative treatment from this patient registry. Where not all patients are started on the new medicine, then it is possible to collect prospective data for the comparative treatment. Where all patients are switched to the new medicine, then the retrospective collection of data will be necessary.
In the event of a specific data collection, the outcomes of the 'value of information'-analysis will determine the focus of the outcomes research.

- As data collection for the comparative treatment is not always involved, the question of randomising to the comparative treatment has not been included in the flow diagram.

Use of different data sources possible

Both in the case of a broad data collection and a specific data collection, data can be obtained from all sorts of sources, such as patient registry studies, quality-of-life studies (with the aid of EQ-5D) and from the literature. Usually the specific data collection does not involve setting up post-registration randomised clinical research or a patient registry. For this reason the emphasis will be on alternative sources of data, and in order to emphasise this, this option has been reflected in the flow diagram.
Alternative sources of data can also include foreign (literature) data. This is possible if the data are representative and usable for the Netherlands. Possible useful studies are: 1) the international follow-up study after the registration study that will supply long-term effectiveness data; or 2) post-registration studies, often initiated at the request of the EMA, which generally focus on obtaining additional safety data, but which can also supply data on clinical effectiveness.

T=4 model

Assessment at t=4

- Assessing the substantiation of cost-effectiveness will take place on the basis of the t=4 model or on the basis of the

results of post-registration randomised clinical research, also known as a 'piggy-back'-study. A 'piggy-back'-study means that, in addition to the usual data, data are also specifically collected that focus on cost-effectiveness.
- Data from outcomes research provide insight into the dynamics of the clinical action.
- On the basis of this, it will be necessary to make adjustments to the t=0 model so that it can be used for determining cost-effectiveness. If the model has not yet been fully developed, then this takes place on the basis of the dynamics of clinical action.
- Data from the outcomes research will subsequently form the input for the t=4 model.
- The results of the model study or the post-registration randomised clinical research will result in determining the medicine's cost-effectiveness.

Substantiation of cost-effectiveness

- It is important to substantiate the cost-effectiveness to the best degree that is reasonably possible.
- The Guidelines for pharmacoeconomic research form the framework to assess the cost-effectiveness.

7.e. Interpreting part II of the flow diagram: determining appropriate use of the medicine and the step-by-step plan

Assessment at t=0

Minimal dataset

- The proposal for the set-up of the outcomes research should also pay attention to establishing appropriate use of the medicine.
- This is possible by collecting a minimal dataset for the medicine.

The period of outcomes research between t=0 and t=4

- The minimal dataset is in part fixed and in part it depends on the indication.
- The minimal dataset contains a number of standard data that we need to collect for every in-patient medicine. The minimal dataset only relates to data for the in-patient medicine and is comprised of Dutch data.
- The data for the minimal dataset, i.e., the data to be collected on the use of the medicine in daily practice (see

section 5), should preferably be collected in a prospective patient registry based on the indication.

Same data source

- In practice, the data for appropriate use and cost-effectiveness can often be obtained from the same data source, i.e., the prospective patient registry based on the indication. This means there is some overlap. As described above, for cost-effectiveness, it is often possible to use various sources of data, whether or not international.

Assessment at t=4

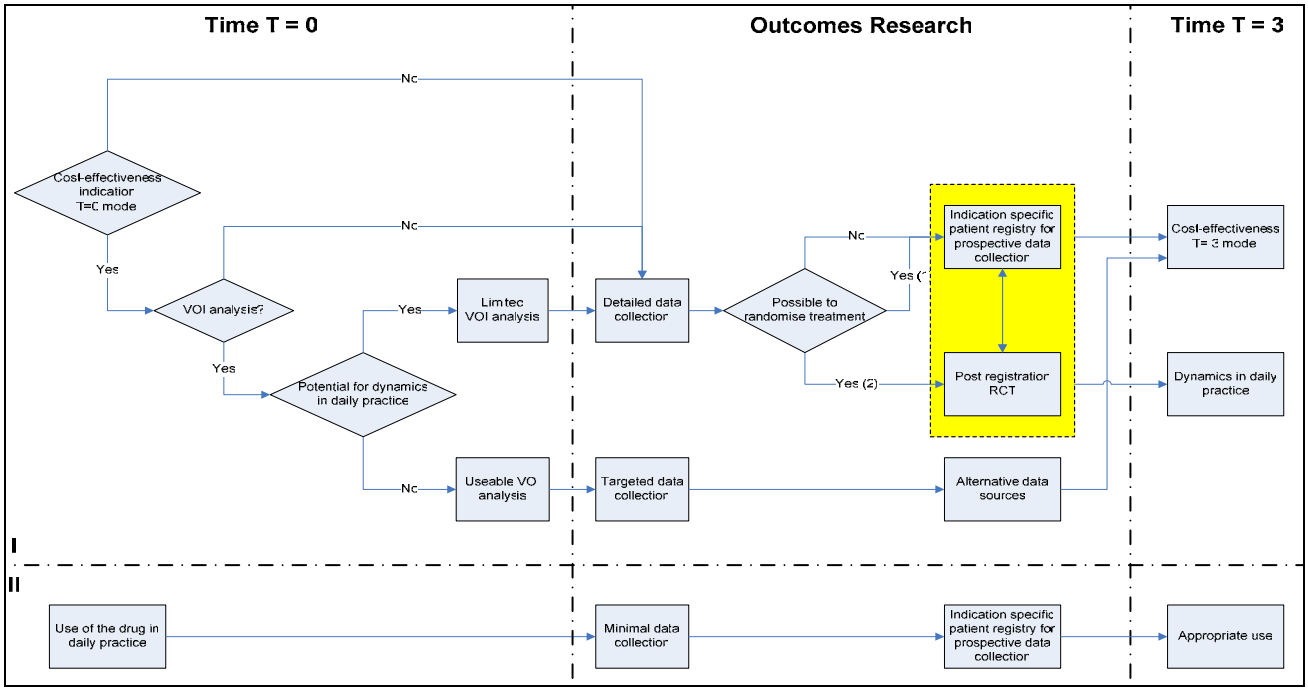
Dynamics of clinical action

- The appropriate use of a medicine can be determined from the data collected in a prospective patient registry.
- The appropriate use of a medicine supplies information about the dynamics of clinical action.

Explanation of the flow diagram

Explanation of figure 4. on the next page:
Flow diagram for setting up outcomes research pragmatically
Upper section, part I – elaboration for determining the cost-effectiveness of a medicine.
Lower section, part II – elaboration for determining the appropriate use of a medicine.
t=0 is the moment the application was submitted;
outcomes research relates to the period between t=0 and t=4, approximately 3.5 years of which will involve outcomes research; ***t=4*** is the moment of assessment

Fig. 4. Flow diagram for setting up outcomes research pragmatically.



7.f. Conclusions

After 4 years assess cost-effectiveness and effective prescription

This section of the 'Guidance for outcomes research' describes a pragmatic set-up for outcomes research, making use of a flow diagram. The point of departure is that four years after temporary inclusion in the policy regulation, it must be possible to make an assessment of the cost-effectiveness and the appropriate use of the in-patient medicine.
The data that are known at the moment of application (t=0) will provide a focus when setting up outcomes research.

Questions to determine direction

The replies to a number of general questions: 'is there a representative and valid t=0 model?'; 'can one speak of dynamics in clinical action?'; 'has a 'value of information'-analysis been carried out?' will make it clear whether a broad data collection or a specific data collection is necessary in order to determine cost-effectiveness.
With a broad data collection, the question arises as to whether randomisation with a comparative treatment is possible, desirable and practically feasible. The professional group should comment on these matters even during the preliminary stages, when compiling the t=0 file, and they should also be actively involved in the outcomes research. In many cases, when setting up outcomes research, preference will go out to a prospective patient registry based on the indication.
With a specific data collection it seems likely that data will be obtained in particular from alternative data sources.
When determining the appropriate use of a medicine, we should always collect a minimal dataset via a patient registry. Where possible, it would be efficient to make use of the same prospective patient registry based on the indication as that from which the cost-effectiveness data are obtained.

Patient registry: practical; valuable; insight into clinical action

Patient registries are practical and valuable sources of data for collecting data for cost-effectiveness and appropriate use. This is not the only reason for setting up patient registries. They are also valuable for providing insight into the dynamics of clinical action. The data provide insight into the treatment of an indication/disease. Those responsible for treatment can optimise therapy on the basis of such feedback information.

Infrastructure

Setting up patient registries requires an efficient infrastructure. Setting up a patient registry should take place

on a regional or a national level. The aim of the data collection, and which data will be necessary, should be clear in advance. The registry should be 'rooted in daily practice' and it should eventually supply data that are useful for clinical practice. An important point for attention is the way in which the observational data obtained are analysed, particularly in view of the expected bias.

Data analysis

A proper infrastructure is also necessary for post-registration randomised clinical research, and here also, attention will have to be given to methods of analysis.

A total of 30 medicines, intended for a variety of indication fields, have been included in one of the NZa policy regulations since 2006. See appendix III for a summary. A patient registry is included in almost all related proposals for outcomes research.

Part V Subsequent steps

8. The four-year period and decision-making

As of December 2010, CVZ will start assessing in-patient medicines for the purpose of decision-making over whether or not to continue inclusion in the policy regulation. The criteria are the actual costs involved and the question as to whether including the medicine is still in the interests of public health from the point of view of therapeutic value and cost-effectiveness[1,2].
This means that from December 2010 on, the 4-year period of outcomes research will have lapsed for the first in-patient medicines, and an assessment of the cost-effectiveness and appropriate use will follow. The following section goes into detail about the four-year period and the decision-making.

8.a. Four-year period

All in-patient medicines

For every in-patient medicine there is a four-year period between the initial assessment – at the time of the application for temporary inclusion – and the final assessment. Outcomes research takes place during this interim period. Opting for a four-year period is based on practical considerations[2]. This is because for most medicines – or registered indications (as the case may be) – during this period it must be possible to collect and analyse the relevant data that are necessary for assessing cost-effectiveness and efficient prescription[3]. CVZ realises that this period may be too short for certain medicines. For example, because it is not possible to collect cost-effectiveness data for a given indication during this period. This is often apparent even at the moment of the application. In these cases CVZ will still carry out an assessment, in accordance with the policy regulations, whereby the advice to

[2] N.B.: A 3-year period was initially chosen. For pragmatic reasons this period has been extended to 4 years. In 2009 it became clear that WMG-parties generally spend a year on logistics and fund-raising before being able to start outcomes research. A 3-year period will be sufficient once the infrastructure has been established

[3] Indeed, 3 years will be sufficient to gather the data once the infrastructure has been established.

the NZa, based on proper arguments, may be that it is desirable to extend this period. It is then up to the NZa to decide on this.

Overview of assessments on CVZ website

All persons involved in an application for assessing an in-patient medicine should be aware of the time-periods, as this will be beneficial to communication and planning and help to avoid uncertainties. CVZ will place an up-to-date summary of in-patient medicines that have been or are being assessed on the CVZ website[3]. The summary will also include, in addition to matters such as the name of the substance, the registered indication and the name of the applicant, the dates for t=0 and t=4 years.
The moment t=0 will be based on the date on which the Board of Management of the NZa makes its decision over the inclusion of an in-patient medicine (substance name and registered indication) in one of the NZa policy regulations on the basis of advice drawn up by CVZ. This will automatically lead to the date for t=4.
The process for in-patient medicines assessed in 2006 is different. The year 2006 was a transitional phase in which CVZ gave parties making the applications more time for drawing up the framework for outcomes research. The t=0 date for medicines submitted in 2006 is the date on which the CFH meeting approved the framework for outcomes research. This also automatically leads to the date for t=4.

8.b. Decision-making

Assessment phase

Appraisal phase

Just as with extramural medicines, for in-patient medicines a distinction can be drawn between an 'assessment' phase and an 'appraisal' phase. The 'assessment' phase relates to assessing the actual costs incurred, the therapeutic value, the substantiation of cost-effectiveness and the appropriate use of the in-patient medicine. The 'appraisal' phase involves the results from the 'assessment' phase, although other factors, such as burden of disease, also play a role. The outcome of the 'appraisal' must be in the interests of public health.

Cost-effectiveness one of the criteria

This means that in decision-making, the cost-effectiveness of an in-patient medicine does not stand alone, but is merely one of the components. For continued inclusion in the policy

regulation, it will first be necessary to fulfil the cost threshold employed by the NZa, which is currently a minimum of 2.5 million euro on an annual basis. Furthermore, it is essential that the in-patient medicine has an added value. Next in line is the assessment of cost-effectiveness and appropriate use. In order to place a value on cost-effectiveness, it is important to have a transparent answer to the question 'What do we regard as cost-effective, or, what is the value of the costs/QALY?'. As stated in the introduction, CVZ does not apply an (absolute) ceiling value for cost-effectiveness. A transparent and tenable evaluation of cost-effectiveness is, however, desirable. CVZ has elaborated on this question in the following report[4].

What is cost-effective?

In order to facilitate decision-making after four years, CVZ will elaborate on reports and file requirements and communicate these to the parties involved in good time.

References

1. Beleidsregel CI-1067 Dure geneesmiddelen
2. Beleidsregel CI-1061 Weesgeneesmiddelen in academische ziekenhuizen
3. www.cvz.nl/ NB. publicatie volgt in de maand december 2008
4. Het pakketprincipe kosteneffectiviteit (achtergrondstudie ten behoeve van de 'appraisal' fase in pakketbeheer) Background study on the 'cost-effectiveness' package principle for the benefit of the appraisal phase in package management. JJ Busschbach and GO Delwel CVZ, November 2010

9. Responses of interested parties

CVZ sent a draft version of this report, for consultation purposes, to the following fifteen interested parties: the *Nederlandse Vereniging van ziekenhuizen* (NVZ); the *Nederlandse Federatie van Universitair Medische Centra* (NFU); the K*oninklijke Nederlandse Maatschappij voor Geneeskunde* (KNMG); the O*rde van Medisch Specialisten* (Orde); the *Stichting Kinderoncologie Nederland* (SKION); the *Nederlands Huisartsen Genootschap* (NHG); the *Nederlandse Vereniging*

van Ziekenhuisapothekers (NVZA); the *Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie* (KNMP); the *Stuurgroep Orphan drugs* (Wgm); the *Nederlandse Patiënten en Consumenten Federatie* (NPCF); *Zorgverzekeraars Nederland* (ZN); *Nefarma*; *BioFarmind*; the *Nederlandse zorgautoriteit* (NZa); the Ministry of Health, Welfare and Sport (VWS).

Based on the responses received, CVZ adjusted a number of points in the "Guidance to Outcomes Research". This section is a global description of the responses of the interested parties together with CVZ's comments.

We received an official response from the Wgm, Nefarma and the NVZ. The responses are included in full in appendix IV to this report.

Summary of responses

Wgm

Status of orphan drugs

The Wgm responded by stating that the 'Guidance to Outcomes Research' contains a lot of useful information. However, information that is useful for orphan drugs and rare diseases is limited. The Wmg made a number of suggestions that illustrate the separate status of orphan drugs and which could bring more balance to the text. The Wmg also argued that in assessing an orphan drug, most attention should be paid to experience in daily practice (outcomes) when treating rare diseases with a (new) orphan drug.

Guidance useful for all in-patient medicines

The 'Guidance for Outcomes Research' was drawn up both for expensive in-patient medicines and for in-patient orphan drugs. The introduction contains an explanation of the expensive in-patient medicines and orphan drugs. We agree with you that certain aspects of the information on orphan drugs could be accentuated. We have included your suggestion about the cost criterion in the introduction and incorporated it into Section 8, as well as incorporating your suggestion relating to problems concerning classification into Section 4. The set-up and the pragmatic approach to outcomes research as described in this 'Guidance' and reflected in the flow diagram in Section 7 can also be used for orphan drugs. Needless to say perhaps, where the report speaks of in-patient

medicines, it is referring to both types of medicines; it is only when we explicitly wish to emphasise the differences that we speak of orphan drugs.

Situation

We are fully aware that in-patient orphan drugs are distinct from expensive in-patient medicines, e.g., with respect to: extremely small numbers of patients; a heterogeneous patient population; high medicine costs per patient; no alternative treatment; it involves the treatment of a (possibly) life-threatening disease for which no alternative treatment possibilities exist. Therefore, in our assessments for the temporary inclusion of orphan drugs in the policy regulation, we expect – for the above-mentioned reasons – that the outcomes research set up for determining the cost-effectiveness of orphan drugs may differ somewhat from outcomes research for expensive non-orphan drugs. When assessing an incremental cost-effectiveness ratio, we will take into account the above-mentioned aspects, as long as they are scientifically substantiated.

Effectiveness data

Like the Wgm, we too are aware of the importance of outcomes in daily practice for orphan drugs. This is why in the introduction we state: 'It is not inconceivable that the substantiation of cost-effectiveness will carry less weight in decision-making on certain in-patient medicines. For example, in the case of in-patient orphan drugs, where appropriate use will probably carry more weight than the cost-effectiveness. It is a known fact that the incremental cost-effectiveness ratio for these medicines will be high[13]. However, this does not mean that these medicines should be excluded, *a priori*, from extra funding. A statement on the cost-effectiveness of these orphan drugs will contribute to consistent decision-making and provide an overview of where funds are going in health care. However, outcomes research for these medicines will focus in particular on obtaining effectiveness data about using a medicine on the right patient population according to the right dose regimen. In order to collect such data for all patients, CVZ feels that it is essential that for rare diseases all patients are included in a patient registry after being diagnosed, so that , e.g., the clinical course of the rare disease, its treatment characteristics and the clinical effects of treatment can be documented.

All patients

In your response you wondered whether orphan drugs can be included in the expensive medicines policy regulation. This is possible. It is possible, if treatment with an orphan drug takes place in a non-centralised location in the Netherlands, which results in the orphan drug failing to meet the cost criterion per hospital as laid down in the policy regulation. One condition is that the cost criterion for the expensive medicines policy regulation is fulfilled. This is possible for rare diseases with a reasonable number of patients in the Netherlands. Treatment then takes place decentralised, both in peripheral and academic hospitals.

Nefarma

Focus on appropriate use

In their response Nefarma claim that the deployment of expensive in-patient medicines must be justifiable. Additional research will therefore be necessary in certain situations. Nefarma does not agree with the approach to outcomes research as described in this 'Guidance for Outcomes Research'. Nefarma feels that outcomes research should only focus on determining appropriate use and not on determining cost-effectiveness, as they regard the very concept as pointless. Nefarma enclosed a proposal for outcomes research that has a lot of similarity with this report, in which they propose that outcomes research focuses mainly on appropriate use and marginally on cost-effectiveness.

Feasibility

Nefarma claims that CVZ has never replied to their letters concerning the methodological aspects of outcomes research. Nefarma suggests that the methodological discussion should take place based on the Nefarma proposal, in the hope of finding a workable solution. Nefarma also claims that all parties involved in outcomes research are wondering whether outcomes research in the present form is feasible.

CVZ feels it is essential that all interested parties are involved in the process of assessing the cost-effectiveness of in-patient medicines. This 'Guidance for Outcomes Research' is the result of the deliberations of CVZ's workgroup on 'Assessing the cost-effectiveness of in-patient medicines' and discussions held with the parties involved via an 'invitational conference'. CVZ's workgroup is comprised of experts from relevant

disciplines and observers from a number of interested parties, including Nefarma (see appendix I). As you are aware, the workgroup focused mainly on content. The methodological points from your letters were included in the discussion and the relevant points have been incorporated into this report.

After 3 years: Cost-effectiveness and efficient prescription

CVZ states that the practical elaboration of Nefarma's proposal for outcomes research reveals many similarities with this Guidance. That is positive. However, there are important differences. CVZ states that Nefarma's proposal has one essential shift in emphasis: primarily addressing appropriate use and where possible also cost-effectiveness. CVZ will always assess the cost-effectiveness and appropriate use of all in-patient medicines within the framework of the NZa policy regulations after three years.

CVZ does not agree with the statement that the concept of establishing cost-effectiveness on the basis of outcomes research is pointless. If this were the case, then the experts in CVZ's workgroup would have drawn this conclusion. Neither is this in line with current international opinions. For example, the 'field evaluations' carried out by order of the Canadian Ministry of VWS in Ontario were partly intended to determine cost-effectiveness. An important attention point is the method of analysing the observational data obtained, especially in view of the expected bias (see Section 6). Also relevant is that cost-effectiveness does not have to be established solely on the basis of data from outcomes research, as relevant data from current clinical research can also be used.

Various criteria play a role in decision-making

CVZ emphasises that decision-making within the framework of the NZa policy regulations will partly be based on assessing cost-effectiveness and appropriate use(see Section 8). Like the other interested parties, CVZ feels it is essential that data on the appropriate use of an in-patient medicine are collected in the outcomes research.

Since 2006 we have assessed a large number of in-patient medicines for temporary inclusion in one of the NZa policy regulations. We have nothing but positive experience of preliminary discussions over to-be-submitted files with applicant parties such as attending physicians and patients.

Experience during preliminary discussions at t=0	The outcomes research submitted give us a great deal of confidence that an assessment after three years is a realistic possibility. We realise that after three years sufficient data will not be available in all cases, e.g., due to the nature of the disease. In such cases as assessment will still take place after three years, whereby the conclusion might be that extending the research period should be considered in order to obtain the desired data. CVZ may take this circumstance into account in its advice to the NZa.
	NVZ
Societal interests	The NVZ subscribes to the societal importance of outcomes research and would like to make a contribution. The main thing is that the research must be feasible at acceptable costs and that it leads to useful results.
Accountability	The NVZ emphasises that they consider it incorrect that the formal responsibility for carrying out (or commissioning) this research has been placed solely on the shoulders of the applicant party – in practice mainly the NVZ – while this party does not have the resources and competences to bear this responsibility.
Coordination	The NVZ, as formal applicant, asks manufacturers to commission/finance outcomes research. The NVZ's role will be to coordinate and mediate. In this function, during the next few years the NVZ will be asking manufacturers about outcomes research that is being implemented. The NVZ also raised a number of methodological points which have resulted in a reluctance on the part of a number of manufacturers to invest in and carry out outcomes research. Lastly, the NVZ suggests that the points mentioned and future financing should be discussed in more detail together with CVZ, VWS and the other interested parties. CVZ endorses the comments of the NVZ. NZa policy regulations and the procedural assessment of in-patient medicines means that the formal responsibility for outcomes research lies on the shoulders of the applicant party, i.e., one of the WMG parties. In practice this will usually be the NVZ. CVZ emphasises, also in this Guidance, that outcomes

Involvement of all interested parties

research should not involve only the applicant. It is essential that all interested parties, such as the applicant, the professional group, the patients' organisation, manufacturers and others, such as health economists and other methodologists, are involved in creating the file and implementing the research.
CVZ's experience of collaboration with the NVZ in these matters is positive. We look forward to seeing the results of the NVZ research and to further collaboration.

College voor zorgverzekeringen

Chairman of the Executive Board

Dr. P.C. Hermans

Appendix 1

List of abbreviations

BMI	- body mass index
CBS	- Centraal Bureau voor de Statistiek [Statistics Netherlands]
CCMO	- Centrale Commissie Mensgebonden Onderzoek [Central Committee on Research inv. Human Subjects]
CFH	- Commissie Farmaceutische Hulp [Medicinal Products Reimbursement Committee]
CLL	- chronische lymfocytaire leukemia [chronic lymphocytic leumkaemia]
CVZ	- College voor Zorgverzekeringen [Health Care Insurance Board]
DBC	- diagnose behandel combinatie [diagnostic treatment combination]
DMARD	- Disease-Modifying Anti-Rheumatic Drug
EMA	- European Medicines Agency
EQ-5D	- EuroQoL 5D, quality-of-life questionnaire
FDA	- Food and Drug Administration
GBA	- Gemeentelijke Basis Administratie [municipal personal files database]
GSB	- GezondheidsStatistisch Bestand [health-related statistical record of CBS]
GVS	- geneesmiddelenvergoedingssysteem [medicine reimbursement system]
HOVON	- Stichting Hemato-Oncologie voor Volwassenen Nederland [Dutch-Belgian Cooperative Trial Group for Hematology Oncology]
HTA	- Health Technology Assessment
HUI	- Health utility index
ICD	- international classification of diseases
IKER/ICER	- incrementele kosteneffectiviteitsratio [incremental cost-effectiveness ratio]
IKZ	- Integraal Kankercentrum Zuid [Integral Cancer Centre of South-Netherlands]
INMB	- incremental net monetary benefit
KEA	- kosten-effectiviteits analyse [cost-effectiveness analysis]
KMA	- kosten-minimalisatie analyse [cost-minimisation analysis]
KUA	- kosten-utiliteits analyse [cost-utility analysis]
KVZ	- Kosten van ziekten [costs of diseases]
LMR	- Landelijke Medische Registratie [national medical registry]
MM	- multiple myeloom [multiple myeloma]
NFU	- Nederlandse Federatie van Universitair medische centra [Federation of University Medical Centres in the Netherlands]
NHL	- Non-Hodgkin lymphoma
NPCF	- Nederlandse Patiënten Consumenten Federatie [Federation of patients and consumer organisation in the Netherlands]
NVZ	- Nederlandse Vereniging van Ziekenhuizen [Dutch Hospitals Association]
NZa	- Nederlandse zorgautoriteit [Dutch Healthcare Authority]
Orde	- Orde van Medisch Specialisten [Association of Medical Specialists in the Netherlands]
QALY	- quality-adjusted life-year
Q-TWiST	- quality-adjusted time without symptoms or toxicity

RCT	- randomised controlled clinical trial
RIVM	- Rijks Instituut voor Volksgezondheid en Milieuhygiëne [National Institute for Public Health and the Environment]
SFK	- Stichting Farmaceutische Kengetallen [Foundation for Pharmaceutical Statistics]
SF-6D	- Short form 6D, quality-of-life questionnaire
UWV	- Uitvoeringsinstituut WerknemersVerzekeringen [Social Security Implementation Body]
VOI	value of information
VWS	- ministerie voor Volksgezondheid, Welzijn en Sport [Ministry of Health, Welfare and Sport]
WMG	- Wet Marktordening Gezondheidszorg [Health Care Market Regulation Act]
ZN	- Zorgverzekeraars Nederland [Health Insurers Netherlands]
ZonMw	- Nederlandse organisatie voor gezondheidsonderzoek en zorginnovatie [The Netherlands Organisation for Health Research and Development]

Appendix 2
Overview of in-patient medicines included in 2006, 2007 and 2008 (January–September)

Name	Indication	Orphan	Applicant
Omalizumab	Severe asthma	-	NVZ
Ibritumomab	Non-Hodgkin lympoma	-	NVZ
Alemtuzumab	Chronisc lymphocytic leukaemia	-	NVZ
Alglucosida alfa	Pompe's disease	+	NFU
Pegaptanib	Macula degeneration	-	NVZ
Infliximab	Colitis ulcerosa	-	NVZ
Infliximab	Psoriasis	-	NVZ
Palifermine	Oral mucositis	-	NVZ
Cetuximab SNHHC	Squamous cell carcinoma of the neck-head region	-	NVZ
Rituximab RA	Reumatoid arthritis	-	NVZ
Rituximab NHL	Non-Hodgkin lymphoma	-	NVZ
Trastuzumab	Adjuvant treatment of breast cancer	-	NVZ
Drotrecogin alfa	Severe sepsis	-	NVZ
Natalizumab	Multiple sclerosis	-	NVZ

Name	Indication	Orphan	Applicant
Ranibizumab	Macula degeneration	-	NVZ
Algasidase alfa	Fabry's disease	+	NFU
Algasidase beta	Fabry's disease	+	NFU
Galsulfase	Mucopolysaccharidois VI	+	NFU
Idursulfase	Hunter's disease	+	NFU
Abatacept	Reumatoid arthritis	-	NVZ
Clofarabine	Acute lymphatic leukaemia in children	+	NFU
Bevacizumab	Metastatic breast cancer	-	NVZ
Bevacizumab	Metastatic lung cancer	-	NVZ
Voriconazol	Invasive aspergillus infection	-	NVZ
Eculizumab	Paroxismal nocturnal haemoglobinuria	+	NFU
Methylaminolevunilaat	Actinic keratosis; basal-cell carcinomas	-	NVZ
Panitumumab	Colorectal carcinoma with EGFR expression	-	NVZ
Bevacizumab	Metastatic renal cell carcinoma	-	NVZ
Anidulafungine	Invasive candidiasis	-	NVZ
Caspofungine	Invasive candidiasis	-	NVZ
Temsirolimus	Advanced/metastatic renal cell carcinoma	+*	NVZ

* Temsirolimus is an orphan drug (registered for the European Union by the COMP/EMEA). The NVZ has submitted an application for provisional inclusion in the expensive medicines policy regulation for which has been approved (see also Section 1).

Appendix 3

Responses of interested parties

Stuurgroep orphan drugs [Dutch Steering Committee on Orphan Drugs] (28106743)
Nefarma (28106750)
NVZ (28111851)