Revision pharmaco-economic guidelines and manual cost research

REPORT FOR ZonMw AND CVZ

M.A. Joore – July 2013

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2. INTRODUCTION

CVZ plans to revise the pharmaco-economic guideline, the guideline outcome research, and the cost manual (all retrievable from www.CVZ.nl). The past years ZonMw, in several programs, has commissioned Health Technology Assessment (HTA) methodology research, of which the results may be valuable for the guideline revision. Furthermore, CVZ has gained experience with some T=4 dossiers, that may indicate a revision of the guideline outcome research specifically. Next to this, ZonMw expressed the wish to obtain information that could inform the evaluation of the HTA methodology programs. In this light, ZonMw, in collaboration with CVZ, commissioned research to extract relevant information for the CVZ guideline revisions and a ZonMw HTA methodology program evaluation from finished HTA methodology projects and T=4 dossiers.

In October 2012 several academic groups in the field of health technology assessment were approached to do a proposition for this research. The timelines were relatively short: start in December 2012 and a project duration of four months.

The HTA research group of the Maastricht University Medical Center and Maastricht University, consisting of the departments Clinical Epidemiology and Medical Technology Assessment (KEMTA) and Health Services Research (HSR) respectively (working together within the research school of Public Health and Primary Care; CAPHRI) was granted the assignment. The deliverable is a report for use by ZonMw and CVZ.

3. METHODS

3.1 Input

ZonMw has funded HTA methodology projects within three programmes: Efficiency, Prevention and Expensive medicines and orphan drugs. Since 2004, in these programmes a total of 36 projects have been funded that are now finalised (January 2013). These projects were divided over three themes: design and analysis (15 projects), cost and outcomes (16 projects) and decision making `(5 projects). See Table 1 for a more detailed overview of the projects per ZonMw program and theme. For each project, ZonMw made available the grant proposal and the final report.

Table 1 Number of HTA methodology projects per ZonMw theme and program

ZonMw Program	**Expensive medicines and Orphan drugs**	**Efficiency**	**Prevention**	**Total**
Number of projects	24	11	1	36
ZonMw themes				
design and analysis	10	4	1	15
cost and outcome	9	7	0	16
decision making	5	0	0	5

CVZ has commissioned HTA methodology research as well. A study on indirect costs by Dr. P. van Baal (Erasmus University) was considered in this project. Because of similarity with one of the ZonMw HTA methodology projects (Expensive medicines and orphan drugs program project 152002022) by the same researcher, this study was analysed together with this project. Furthermore, CVZ commissioned a pilot study on the outcome research for expensive medicines, linked to the dossiers of bortezomib (Velcade) and oxaliplatin. In addition four finalised expensive medicines outcome research dossiers were available: agalsidase alpha (Replagal) and agalsidase beta (Fabrazyme) for Fabry's Disease, alglucosidase alpha (Myozyme) for Pompe's Disease, omalizumab (Xolair) for persistent asthma, and ranibizumab (Lucentis) for macula degeneration.

3.2 Procedure

The following procedure was followed:

1. A form was developed to be used as a data extraction tool for relevant information from each project dossier and T=4 dossier. The form contained the following information fields:
    a. A brief summary of the objective, methods and results of the project.
    b. An overview of the scientific output:
        i. Knowledge and insights, possibly leading to scientifc output (publications, presentations),
        ii. Instruments: questionnaires and tools such as manuals, checklists, algorithms, models et cetera.
    c. A scoping review: as some of the projects had finished several years ago a (in light of limited time available) non systematic review of recent relevant developments in relation to the project was performed.
    d. Relation to phamaco-economic guideline, guideline outcome research and the cost manual
        i. Chapter/section of the guideline the project relates to was noted,
        ii. Score whether revision / research / both / neither seemed indicated,
        iii. A justification for the scores,
        iv. If indicated, a suggestion for (the direction of) revision and / or research.

2. Each project and T=4 dossier was assigned to two persons from the project team who completed the form together.

3. All completed forms were discussed in the project team to reach consensus.

4. Based on the completed forms a concept report was composed to provide an overview of the extracted information per ZonMw program and ZonMw theme, as well as per CVZ guideline chapter. The completed forms are included in the report as appendices.

5. Finally, the concept report was discussed in the project team.

4. RESULTS HTA METHODOLOGY RESEARCH

All completed project forms, containing a summary, overview of output, results of the scoping review as well as indications for revision and/or research, are in the appendix.

4.1 Output per ZonMw program

Thus far, a total of 47 publications, 17 publications in preparation and 39 presentations can be considered output of the HTA methodology projects. It should be taken into account that the projects from the Expensive medicines and orphan drugs program had finished only recently, in comparison to the projects from the Efficiency and Prevention program. As a result, the number of publications and presentations coming from this program may increase in the future. Furthermore, it becomes apparent that the projects in the Expensive medicines and orphan drugs program relatively more often than the other two programs, delivered instruments such as questionnaires, tools and models. See Table 2.

Table 2 Scientific output per ZonMw program

	Expensive medicines and orphan drugs	**Efficiency**	**Prevention**	**Total**
	24 projects	*11 projects*	*1 project*	**36**
Knowledge/insights				
publications	25	19	4	48
publications in preparation	14	3	0	17
presentations	17	22	0	39
Instruments				
questionnaires	2	1	0	4
tools	14	2	0	16
models	1	2	0	3

The three questionnaires developed in the HTA methodology projects are the following:

- A modular questionnaire (“iMTA Valuation of Informal Care Questionnaire”) and manual on measurement and valuation techniques for the inclusion of informal care in economic evaluations (project 152002009, Expensive medicines and orphan drugs program),
- Versions of the experience sampling method and the day reconstruction method for use in the economic evaluation in health care. (project152002020; Expensive medicines and orphan drugs program),
- English and Dutch versions of TiC-P (including an electronic version), and manual with SPSS syntax (project94506414, Efficiency program).

Three decision models were listed as output of the projects:

- A micro simulation model to assess the optimal treatment strategy for severe haemophilia (in Matlab scripting language). (project 152002004; Expensive medicines and orphan drugs program),

- A discrete Event Model using a real world example, i.e. pediatric ultrasound screening for hip dysplasia. (project 94516309/IMP; Efficiency program),
- A mathematical model that is able to correct the long run incremental net benefit for short run inefficiencies (available upon request). (project 1708830019; Efficiency program).

A total of 16 tools have been developed in the HTA methodology projects. This ranged from checklists, to frameworks or algorithms. A description of the tools can be found in Table 3.

Table 3 Overview of tools as output of ZonMw HTA methodology projects

Program & Project	Tools
Expensive medicines and orphan drugs	
152002005	Flow diagram to decide what analyses should be performed to identify the need for additional research.
152002006	Manual for a mixed treatment comparison cost-effectiveness (MTC-CE) tool.
152002007	Checklist to frame a health technology assessment study.
152002010	Correction model for discounting health state valuations derived with TTO.
152002013	Algorithms (syntax) and manuals for the three disease specific questionnairesto derive utilities.
152002017	Decision support tool that provides guidance for the selection of the most appropriate method for bias reduction in cost-effectiveness analyses based on observational studies.
152002018	Decision tree to help decide whether to include or exclude productivity costs in economic evaluations
152002021	- Framework to systematically explore which sources and input parameters might be relevant to acknowledge patient heterogeneity - Overview of methodologies to acknowledge patient heterogeneity in the design, analysis and presentation phase of an economic evaluation. - Checklist to help national guideline authorities to formulate comprehensive recommendations with regards to acknowledging patient heterogeneity in economic evaluations.
152002022	PAID 2.0 R tool to calculate indirect costs within health care, description of the technical background and a manual.
152002025	Prediction model for extrapolating treatment effects as found in phase II/III clinical trials in Rheumatoid Arthritis daily clinical practice.
152002026	Guidance document on how to use predictive markers
152002027	Software (in R) for inverse probability weighting and G-computation by means of Huang joint model.
Efficiency	
1708856019	Checklist researchers can use in future test evaluations to identify potential patient related effects of testing that should be considered as additional endpoints.
1709925039	Procedures for dynamic updating of prediction models (R code).

It should be noted that not all instruments were fully validated (as stated by the researchers). Also, not all instruments were freely available or easily accessible. Details on the validity and availability/accessibility can be found in the project forms in the appendix.

4.2 Project information in relation to the guidelines

The results of the HTA methodology projects frequently indicated revision of the pharmaco-economic guideline or guideline outcome research. In a majority of the projects, at the same time, further research was indicated. A smaller number of projects had results that indicated a revision of the cost manual. See Table 4.

Table 4 Number of projects indicating guideline revision and/or research per ZonMw program

	ZonMw program			
CVZ Guideline	**Expensive medicines and orphan drugs** *24 projects*	**Efficiency** *11 projects*	**Prevention** *1 project*	**Total**
Pharmacoeconomic guideline				
Revision indicated	4	1	0	**5**
Research indicated	3	4	0	**7**
Both revision and research indicated	14	1	0	**15**
No revision nor research indicated	3	5	1	**9**
Guideline outcome research				
Revision indicated	5	0	0	**5**
Research indicated	1	2	1	**4**
Both revision and research indicated	13	1	0	**14**
No revision nor research indicated	4	8	0	**12**
Manual cost research				
Revision indicated	3	1	0	**4**
Research indicated	0	1	0	**1**
Both revision and research indicated	4	0	0	**4**
No revision nor research indicated	17	9	1	**27**

Table 5 provides a more detailed overview of the relation between the HTA methodology projects and the chapters in the three guidelines.

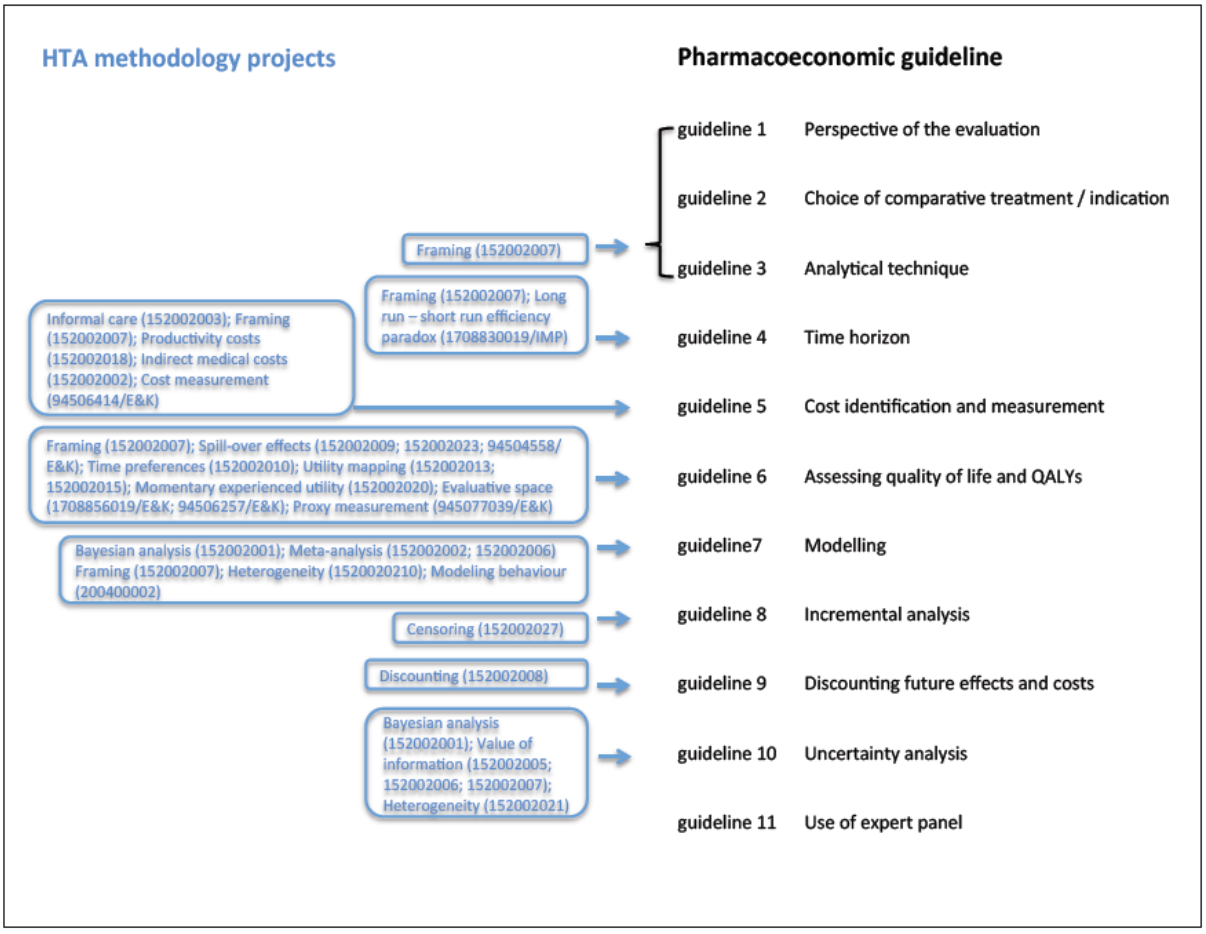
Four projects were found to not directly apply to a chapter in the pharmaco economic guideline. Two projects focused on methodology to assess clinical effectiveness (152002025, 152002026). This is not a part of the guideline, but as the health economic evaluation builds on clinical effectiveness, developing guidance on this topic could certainly be considered. One project (152002017) focussed on correction techniques for confounding bias in costs and outcomes, while data analysis is not part of the pharmaco economic guideline. Another project investigated the use of registries for economic evaluation (152002012). These four projects do relate to the guideline Outcome Research and are discussed in that paragraph. Three projects did not relate to any of the three guideline-documents. Two projects focused on decision-making (equity (152002011) and allocation (152002019) considerations) while the guidelines are on conducting an economic evaluation. Another study investigated the use of conjoint analysis to determine barriers and facilitators for implementation to inform the optimal design of an implementation strategy (94514411/IMP), while development or evaluation of implementation strategies is not part of the guidelines. The results of these

projects did not indicate further research either. In addition, five projects did not seem to focus on HTA methodology development (in light of the guidelines defined as: the development of methods to evaluate health care). Two projects provided an example of an application of the elicitation of patient preferences using discrete choice experiments (94514010/IMP, 945077309/E&K). Another project investigated the development of a clinical prediction rule to inform medical decision-making (1709925039/E&K). Another example is a project that applied decision modelling to select treatment strategies in haemophilia (152002004). Project 94516309HTA/IMP provided an example of the usefulness of initial (early) modeling before implementation of a health care programme. However, no new (modeling) methodology was developed or tested. These 8 projects are not considered in the following chapters.

4.2.1 Pharmacoeconomic guideline

In this paragraph, for the 24 projects relating to the guideline, the findings per project are discussed per chapter of the pharmacoeconomic guideline. Projects related most often to Chapter 6 'Assessing quality of life and QALYs' (11 projects). Each section starts with a table with an overview of the relevant projects per guideline chapter, and the recommendation (revision, research or both).

Figure 1 HTA methodology projects in relation to the pharmaco-economic guideline



Guideline 1: Perspective

Project	Topic	Recommendation
152002007	Framing a health technology assessment	REVISION

Project 152002007 investigated the framing of a health technology assessment. Framing is not considered in a separate chapter in the guideline but is addressed in chapter 1 to chapter 7. This project developed a checklist to systematically frame HTAs for resource allocation decisions in a way that they are applicable to the decision problem. The checklist consists of eleven factors: objective, audience, perspective, population, comparators, clinical practice, time horizon, consequences, patient use, professional use, and price and resource use. The study also provides a practical example of the applicability of the checklist. A suggestion for revision of the guidelines could be to recommend the use of the checklist to frame the evaluation. Alternatively, the checklist could serve as a starting point to develop a guideline chapter specifically on framing / scoping the economic evaluation.

In addition, a number of projects investigated topics that link to the perspective of an economic evaluation. Project 152002020 challenged the societal perspective by exploring the use of momentary experiences of patients to obtain health state utilities instead of societal preferences derived using choice-based methods. Two projects investigated the broadening of the 'evaluative space' to outcomes broader than (or different from) health related quality of life: 94506257/E&K, 1708856019/E&K.These projects are discussed under guideline 6: assessing quality of life and QALYs. Four projects investigated the inclusion of spill-over effects in other persons than the patient: in caregivers (152002003, 152002009), significant others in general (152002023) or the child (94504558/E&K). These projects are discussed under guideline 5: Cost identification and measurements or guideline 6: assessing Quality of life and QALYs.

Guideline 2: Choice of comparative treatment

Project	Topic	Recommendation
152002007	Framing a health technology assessment	REVISION

Project 152002007 is described under guideline 1.

Guideline 3: Analytical technique

Project	Topic	Recommendation
152002007	Framing a health technology assessment	REVISION

Project 152002007 is described under guideline 1.

Guideline 4: Time horizon

Project	Topic	Recommendation
152002007	Framing a health technology assessment	REVISION
1708830019/IMP	Long run - short run efficiency paradox in health care	REVISION

Project 152002007 is described under guideline 1.

Project 1708830019/IMP investigated the long run – short run efficiency paradox. Standard CEA considers differences in costs and effects between alternative medical innovations to be constant over these innovations' respective lifetimes. This means that average costs and effects found in the trial or study period are assumed to be representative for the average costs and effects over the technology's lifetime. In the long run, the technology's costs and effects can indeed be expected to reach or approximate such a steady state. However, the assumption of constant marginal cost-effectiveness outcomes is an idealization and is not very realistic as it neglects the short run where the old and new technology often co-exist. In the short run, cost-effectiveness may deviate considerably from the outcome of a conventional economic evaluation. In this project these deviations are quantified and their implications discussed. Failing to acknowledge short run aspects in cost-effectiveness analysis may raise doubts about the validity of its outcome, and may also lead to disappointment with economic evaluations in general, as evidence on cost-effectiveness is of less interest to decision makers who are focusing on the short run. The authors developed a model to correct the long run incremental net benefit (INB) for short run inefficiencies and applied it to two cases: 1) In-hospital haemodialysis substituted by Continuous Ambulatory Peritoneal Dialysis (CAPD) and 2) digitizing a radiography system. The cost manual already refers to part of the work of the authors on page 89. However, this project has resulted in a final model. It seems indicated to revise the pharmaco-economic guideline using the final outcomes of this project (and to revise the cost manual accordingly).

Guideline 5: Cost identification and measurement

Project	Topic	Recommendation
152002003	Informal care	REVISION & RESEARCH
152002007	Framing a health technology assessment	REVISION
152002018	Productivity costs	NO REVISION NOR RESEARCH
152002022[1]	Indirect medical costs	REVISION & RESEARCH
94506414/E&K	Cost measurement	RESEARCH

Project 152002003 investigated the monetary valuation of informal care. In the guideline it is mentioned that time-costs of informal caregivers should be incorporated in economic evaluations from the societal perspective. The manual cost research describes more in detail how to incorporate certain costs and in the pharmaco-economic guideline a referral is made to the manual cost research. In the manual for cost research it is recommended to use the proxy good method for the valuation of informal care in economic evaluations. However, if informal care plays an important role in the care program under evaluation, health effects in

[1] And Academia II report on indirect medical costs by the same researchers

informal caregivers can be measured. Furthermore, a non-monetary valuation instrument (the example of the CarerQol is mentioned) can be used to measure well-being and the burden of informal care. The researchers state that in the current project they developed an instrument that includes a monetary pillar but also the construct “well-being”. From this perspective they recommend adaptation of the manual cost research, and indirectly through this the pharmaco-economic guideline, and incorporate the well-being valuation method as a method to determine costs of informal caregiving. The researchers show the validity of the construct well-being in providing informal care and recommend adaptation of the manual cost research and guideline, based on their results. However, the debate on whether outcomes should focus on health or health and beyond is not limited to informal care but is topical in economic evaluations in general. It requires a normative change of position to incorporate well-being as an outcome. Furthermore, thenormative discussion on whether or not income should play a role in the valuation method seems warranted, as including this factor means that a higher income possibly means a higher hourly tariff. The researchers mention several suggestions for further research with respect to the validity of the well-being valuation method, namely further dividing the hourly tariffs based on other characteristics.Further research should also focus on the possibilities for and implications of using the construct well-being instead of health related quality of life in valuations of informal care in economic evaluations.

Project 152002007 is described under guideline 1.

In project 152002018 it is argued that if a societal perspective is taken, productivity costs should only be ignored in economic evaluations if it is expected in advance that productivity remains relatively unaffected based on patients’ age or their ability to work before and after treatment. This is already in line with the Dutch pharmaco-economic guidelines where a societal perspective including all relevant costs and benefits are recommended.

Project 152002022 studied indirect medical costs. The guideline mentions 4 categories of costs, including indirect medical costs within the health care sector. Indirect medical costs not related to the treatment or intervention should not be included on the economic evaluations. In the project a standardized method was developed for incorporating indirect medical costs not related to the treatment or intervention. The authors of the project and the Academia II report recommend to change the guideline, and state that indirect medical costs not related to the treatment and intervention should be incorporated in economic evaluations (the Cost Manual text is not in line with the pharmaco-economic guideline, the former which advices to use PAID for calculating unrelated medical costs). Incorporating unrelated indirect medical costs in economic evaluations may have an impact on the cost-effectiveness of health technologies in certain populations. It should be noted that, consequently, there may be an incentive for strategic behavior of technology developers (e.g. pharmaceutical companies) to focus their R&D to quality of life enhancing interventions, as they have more potential to be cost-effective (and receive a positive coverage decision) in comparison to life extending interventions. Two issues require further investigation or require attention when implementing. First, if indirect medical costs not related to the treatment will be incorporated, it still remains unclear how indirect costs not related to the treatment outside the health care sector in added life years should be considered. The same question exists for direct costs outside the health care sector in added

life years. Second, much focus is now directed at estimation of unrelated indirect medical costs and surrounding uncertainty. It can be argued that estimation of long term QALYs in decision models should be handled with the same scrutiny. This argument is however not an impediment for revising the guideline as it regards unrelated medical costs.

Project 94506414HTA/E&Kstudied the validity and reliability of the condition-specific questionnaire on healthcare consumption, illness and work (TiC-P). This questionnaire is mentioned in the cost manual as a questionnaire that could be used to measure resource use in a population with psychological problems. The validity was generally satisfactory, although the measurement of presenteeism may require additional research. In addition, the recent work of M. Krol (PhD dissertation;Productivity costs in economic evaluations, Erasmus University Rotterdam) may be taken into account.

Guideline 6: Assessing quality of life and QALYs

Project	Topic	Recommendation
152002007	Framing a health technology assessment	REVISION
152002009	Spill-over effects: informal caregivers	REVISION & RESEARCH
152002023	Spill over effects: significant others	REVISION & RESEARCH
94504558/E&K	Spill-over effects: child	RESEARCH
152002010	Time preferences in time trade off	REVISION & RESEARCH
152002013	Utility mapping	REVISION & RESEARCH
152002015	Utility mapping	REVISION & RESEARCH
152002020	Momentary experienced utility	RESEARCH
1708856019/E&K	Evaluative space: patient effects of testing	RESEARCH
94506257/E&K	Evaluative space: outcomes beyond health	REVISION & RESEARCH
945077039/E&K	Proxy measurement	RESEARCH

Project 152002007 is described under guideline 1.

Three projects investigated spill-over effects in persons other than the patient: 152002009, 152002023 and 94504558:

- Project 152002009 studied the CarerQol. The developing and testing of instruments such as the CarerQol to identify, measure and value all the relevant aspects of caregiving is in line with the guideline, which requires the inclusion of all cost and benefits “irrespective of who actually bears the costs or receives the benefits” (CVZ, 2006). As such, the findings of this project do not warrant revision. However, the guideline could be more specific about which spill-over effects should be considered (e.g. QALY or beyond), in whom should these effects be measured and how should these effect be reported in economic evaluations (see also project 1520022023). By including the valuation step, the instrument may also take up societal preferences; which the current project has tested in practice. The use of such measures in economic evaluations in combination with patient’s health related quality of life measures remains questionable because of the non-compatibility and possible double counting issues. The instrument may report not only carer’s subjective well-being but may also take into account that of the patient and therefore double counting may take place. Future research could look at ways on to avoid such double counting error in cost-utility analyses. In this respect project 152002003, on the

monetary valuation of informal care (described under guideline 5), is also of relevance in the sense that if spill-over effects are included on the effect side of the ICER, there is a danger for double-counting when (parts of) spill-over effects are also included on the cost side (and vice versa).

- Project 152002023 investigated the effect of significant others in utility values. The current pharmacoeconomic guidelines advocate a societal perspective, which means that effects on significant others – when relevant – should be included in economic evaluations. As such, the findings of this project do not warrant revision. From the guidelines it is however not clear 1) what types of effects should be included, i.e. health effects (QALY) or broader effects (beyond the QALY), 2) in whom these effects should be measured and 3) how these effects should be reported in economic evaluations / integrated in incremental cost-effectiveness ratios. With regard to (1), the decision for revision mainly depends on the normative standpoint taken (what is the maximand, health or broader then health) and on the question whether the same concept should be maximized in both patients and significant others. With regard to (2), it can be suggested that significant others at least include informal caregivers, as it is known that they may experience mental, physical and/or financial problems. More research is needed to check if similar noteworthy effects are also present in e.g. family members. With regard to (3), *before* the guideline is revised it seems indicated that especially on the subject of utility interdependence/double counting more research is performed. The researchers suggest that overall there is no effect on health state valuation, but depending on what is considered (effects on others due to shorter duration of life or worse quality of life) health state valuations are increased or decreased. So, there actually exists a danger for double counting although the authors conclude that it middles out over respondents. More research on this subject seems warranted in order to reproduce the results from this study. The same phenomenon may arise if (health) effects in significant others are measured or valued, in that significant others (or the general population in case of valuation) may also include effects on the patients in their own measurement/valuation. Furthermore, the focus in this study has been on spill-over effects regarding valuation. Little emphasis has been put on spill-over effects in the measurement of health states in patients/significant others themselves (i.e. the descriptive part of instruments such as the EQ-5D). E.g. the mood dimension may be sensitive for including effects on significant others. When these effects are also measured in the significant other there is a danger for double counting. Until these issues are solved, health/wellbeing effects on significant others (as discussed under (1) and (2)) can at best be reported separately. Related to this project, project 152002003, on the monetary valuation of informal care (described under guideline 5), is also of relevance, in the sense that if spill-over effects are included on the effect side of the ICER, there is a danger for double-counting when (parts of) spill-over effects are also included on the cost side (and vice versa).
- 94504558/E&K investigated the specific spill-over situation in pregnant women (or more generally in Obstetrics & Gynaecology), where QALYs are not only about quantity and quality of life of the mother, but also about the quantity and quality of the life of the (unborn) child. Current utility measurements (EQ-5D, SF-36 and HUI) do not capture this. Revision of the guideline does not seem indicated for this specific case. Further research could focus on how to deal with situations in which the QALY

is or should be determined by the quantity and quality of life of not only the 'patient' but also a directly involved other, as in the situation of pregnant women and their unborn child. Also the extent to which other methods for estimating preferences are possible, and to which extent these can be used as a replacement for the conventional QALY or joined with the conventional QALY, warrant research.

Project 152002010 investigated time preferences in relation to time trade off (TTO) health state valuations. The study clearly showed that time preferences are influential in estimating utility using TTO and that this can be corrected by the direct method. However part of the studies were done in student populations. Broader testing in patients groups seems indicated before revision of the guidelines. The principal investigator (A. Attema, Erasmus University) is involved as a co-applicant in a new study funded by the ZonMw Expensive Medicines and Orphan Drugs HTA methodology program: Test of lead time TTO in the general population, 152002039). In the long run, correcting TTO scores for time preference could be part of guideline, and this could be done using the direct method.

Project 152002013 and project 152002015 investigated ways to derive health state utilities from disease specific instruments (also referred to as 'utility mapping'). The guideline mentions that ahealth state utility can be obtained in three ways: 1) by means of EQ5D measures in patients, valued with the value-set derived from the general population;2) own valuations by means of the common valuation methods (standard gamble, TTO and VAS); or 3) apply valuations from previously published results. The use of disease specific data (with mapping or with valuation) is not mentioned. In literature several methods are described when using disease-specific measures for health state utilities.

- Based on the results of project 152002013, mapping was the best alternative (for the three questionnaires under study), and could be recommended as one of the methods to derive health state utilities from a disease specific instrument. However, in the project only three disease-specific questionnaires were studied and for many others results remain unknown.
- Project 152002015 developed an algorithm to predict health state utilities from the QLQ-C30. However, the final algorithm is not yet available, and the researchers advise to use the current one with caution. In the international literature alternatives to mapping are mentioned and aspects that should be taken into consideration. In the guideline it should be clearly stated under which conditions the use of disease specific instruments is allowed and which requirements are made with respect to the methods used to obtain utility values. Suggestions for further research include: study other questionnaires, generalizability to subtypes of the conditions under study and the choice of model and type of analysis for mapping.

Study 152002020 focused on the way utilities are obtained by using momentary experiences of patients to obtain health state utilities instead of societal preferences. This brings a novel approach in emphasizing the differences between a 'classical' health utility obtained by means of traditional methods based on choices (SG, TTO), and 'experienced' utilities obtained by means of the 'experience sampling method (ESM) and the 'day reconstruction method' (DRM). The project results indicated that the ESM and DRM were feasible. The study focused on three aspects of quality of life: positive affect (PA), negative affect (NA), physical complaints (PC) and overall health. ESM and DRM only seemed to have similar

results for affect. While the results for other domains appear to be comparable, the study has shown that the relative impact of mental health problems in everyday life is underestimated in QALYs based on retrospective measures (e.g. EQ-5D, VAS) or prospective ones (e.g. TTO). The study results indicate that the use of these QALYs to the allocation of resources is unlikely to lead to maximum benefits. As this study is the first to investigate the momentary measurement of experienced utilities, more research seems warranted before guideline revision is indicated. Further research is for instance needed to determine whether the ESM and DRM also converge in measuring physical symptoms and overall health. In addition, more research is needed to investigate the potential value of momentary experienced utility in health care coverage. The study does however add to the already considerable literature that questions the way QALYs are determined. Momentary measures could be an alternative. Discussion on the subject seems warranted.

Two projects investigated the broadening of the 'evaluative space' to outcomes broader than (or different from) health related quality of life: 1708856019/E&K and94506257/E&K.

- Project 1708856019/E&K investigated additional patient effects of testing. Although the researchers have shown that, according to healthcare professionals and patients, additional effects of medical testing do exist, they have not yet investigated how large the effects are, whether these are clinically relevant, or significant for decision making, and generalisable to other situations. Therefore, revision does not seem indicated at this point. Besides the aforementioned issues, further research could focus on how the additional outcomes could be incorporated in health assessments and thus be considered in decision making. This was one of the objectives of the original grant application, but it was not addressed in the final report.
- Project 94506257/K&E showed, using discrete choice modeling, that acknowledging patient preferences for health as well as outcomes beyond health (e.g. aspects not fully captured in the QALY) may lead to different results than a focus on preferences for health alone. At the moment, patient preferences for outcomes beyond health are not mentioned in the Guideline Outcome Research or the FE guideline. Questions regarding the place of patient preferences in decision-making and the way these preferences should be elicitated (by whom, when, about what) are indicated. Regarding the potential relevance for decision making of patient preferences for outcomes beyond health as shown in this project, and the growing evidence available on this matter, it might be indicated to explicitly include patient preferences as a relevant source of information in the guidelines. Research regarding the place of patient preferences in decision making is currently underway. Further research is indicated regarding the way patient preferences to inform resource allocation decisions should be elicitated: by whom and when (perspective), and about what (evaluative space).

945077039/E&K studied proxy measurement. The guideline states that the health state descriptive system that is used could be completed either by patients or by proxies, but does not specify in what situations and how this should be done. The project took several perspectives on proxy measurement (measurement and valuation, disease-specific and generic health-related quality of life, Thurstone scaling versus VAS for valuation, measurement of health-related quality of life of the caregiver, etc.) and did not have one particular focus. The researchers themselves recommend further research. Therefore,

although the guideline could be more specific about when and how proxy measurement should be applied, the current project does not give rise to immediate revision. Suggestion(s) for further research:
In the current project proxy measurements were compared with patients' self-assessment of HRQoL. It is not clear yet in what situations patients' self-assessments are valid for the purpose of economic evaluation and healthcare decision-making, and – supposing that they are valid - how ((non)-systematic) differences between patient and proxy measurements should be handled/reported in economic evaluation. Furthermore, more research about how the proxy measurement should best be performed (i.e. by the proxy patient or proxy-proxy perspective) and by whom seems warranted. Health state descriptive systems should comply with and be validated for the method of proxy measurement.
The project does not provide information on the generalizability of results to other conditions or populations (e.g. children) in which proxy measures might be appropriate. Before the PE guidelines/Guideline Outcome Research can be made more specific about proxy measurement, such information would be useful. As many reviews on the topic have already been published, in several populations, a meta-review addressing some of the abovementioned research questions might be useful.

Guideline 7: Modeling

Project	Topic	Recommendation
152002001	Bayesian analysis	REVISION
152002002	Meta-analysis	REVISION & RESEARCH
152002006	Meta analysis and Value of Information	REVISION & RESEARCH
152002007	Framing an economic evaluation	REVISION
152002021	Heterogeneity	REVISION & RESEARCH
200400002	Modeling behavior	NO REVISION NO RESEARCH

Project 152002001 compared a Bayesian and a Frequentist approach for analysis and synthesis of evidence from multiple, heterogeneous sources Bayesian statistics. Bayesian statistics is currently common practice and often used for performing economic evaluations. It offers advantages in analysing and interpreting the results. Therefore, it might be considered in the pharmacoeconomic guideline. A Bayesian approach, possibly in addition to a Frequentist approach, could be requested or suggested for the analysis, interpretation and presentation of the results this chapter on modelling, as well as in Chapter 10 "Uncertainty analysis". The project topic was very broad and frequently described in the literature. Therefore, it is difficult to provide specific recommendations for further research.

Project 152002002 provides an overview of synthesizing methods, and recommendations for the use of these methods. The project also illustrated that the choice of a synthesizing method impacts the results. The project's findings suggest the inclusion of a number of recommendations on data synthesis in the guidelines. In general, as indirect methods are clearly outperformed by the mixed treatment comparisons, if direct evidence is available this should always be used, either in direct meta-analyses or in mixed treatment comparisons. When there are indications of potential differences between trials, it is recommended to conduct sensitivity analyses to investigate whether the health-economic outcomes are affected by the choice of meta-analysis. When all trials seem to be drawn from the same

underlying population fixed-effects models are generally preferred because of the smaller bias and mean absolute deviance compared with random-effects models. When more than one parameter is estimated from the same set of sources and the statistics (e.g. I2) indicate that the data are homogeneous for one parameter, but heterogeneous for another, it is recommended that all parameters are calculated using the same type of model. The model type selection should be based on trial heterogeneity rather than parameter heterogeneity. The methods by Song, Puhan and Lu/Ades (fixed effects) are suggested for mixed treatment comparisons.Network coherence should be examined when using mixed treatment comparisons.When a Weibull distribution is a suitable parameterization of the survival curve, the method by Arends is preferred to estimate entire survival curves, instead of estimating separate probabilities at each point in time.
ISPOR's Task Force on Indirect comparisons presses for more research to extend the methods into further areas of secondary analysis, such as synthesis of multiple correlated outcomes and covariate adjustment, or meta-regression, while recognizing the difficulties of reliable covariate adjustment in the sparse data sets usually available.2,3 In addition, further research might also focus on which synthesizing method(s) should be used in what situation and on quantitatively weighing evidence based on its quality (e.g. according to GRADE criteria). Quantitative weighing has a strong element of arbitrariness concerning the magnitude of the weights. Therefore, further research might develop a systematic approach to weighing evidence considering for example different weighing schemes, the same weights for all evidence and excluding the source(s) of evidence with a (too) low quality.

Project 152002006 also focussed on data synthesis; specifically a new method for mixed treatment comparison and value of information. These methodologies are useful when performing economic evaluations and could certainly be considered in the revised guidelines. However, the role of the newly developed mixed treatment comparison method in this project is not entirely clear based on the information supplied. Based on this project as well as project 152002002 it is indicated to suggest in the guideline to synthesize all relevant evidence and compare multiple comparators, if indicated. Value of information analysis is common practice in health technology assessment and can thus be considered in the revised pharmacoeconomic guideline as well. Further research to examine more thoroughly the role of the newly developed mixed treatment comparison method compared to standard methodologies (e.g. by Lu and Ades, Song, Puhan) seems indicated as well.
Project 152002007 is described under guideline 1.

Project 152002021 investigated patient heterogeneity. The project resulted in a framework to systematically explore which sources and input parameters might be relevant to acknowledge patient heterogeneity. Also, an overview of methodologies to acknowledge patient heterogeneity in the design, analysis and presentation phase of an economic evaluation was developed. Furthermore, a checklist to help national guideline authorities to formulate comprehensive recommendations with regards to acknowledging patient heterogeneity in economic evaluations was presented. Patient heterogeneity is currently not explicitly considered in the guideline. However, especially when there are large dynamics in daily practice, acknowledging patient heterogeneity might be valuable. Guidance based on the project's insights, recommendations and developed instruments (the overview of methods, the framework and the checklist; see output section) could be incorporated in the modelling chapter or in the chapter considering uncertainty analysis (as patient

heterogeneity can be considered as a type of uncertainty). The selection of patient subgroups, particularly in case multiple (continuous) variables are considered simultaneously, may require further methodological research.

Project 20042000002 developed an innovative methodology for cost-effectiveness analysis (CEA) in behavioral change interventions. Often behavioral change is a dynamic process. Therefore, assessing long-term effects is important. This is difficult and expensive, and as a result such data are often not available. In the heart of the project lies the development of advanced CEA modeling strategy that can be applied to interventions for different health behaviors; which is validated and tested in the existing datasets of behavioral interventions, aimed at quitting smoking. The simulated CEA showed largely similar, but somewhat more conservative, results and was therefore validated by the true data. Using self-efficacy to enhance the estimation of the true behavioral outcome seems a feasible and valid way to estimate future cost-effectiveness outcomes. This study showed that modeling of future behavioral change in CEA of a behavioral intervention further strengthened the results of the standard CEA. Ultimately, modeling future behavioral change could have important consequences for health policy development in general and the adoption of behavioral interventions in particular. Revision of the pharmaco-economic guideline does not seem indicated because pharmaceuticals usually do not play a role in behavioural change interventions. The feasibility of these kinds of models need to be tested looking at other behavioral change interventions.

Guideline 8: Incremental analysis

Project	Topic	Recommendation
152002027	Censoring	RESEARCH

Project 152002027 investigated censoring. When estimating a cost effectiveness ratio in a randomized trial with a cumulative survival (time-to-event) endpoint, adjustment for informative censoring (dropout of follow-up due to reasons that are also associated with the outcome) is necessary. This applies to the estimate of effects, but also to the cost estimates. For adjustment of cost estimates, methods are available and have been evaluated, but for effect estimates this is not the case. In this project, the authors compared inverse weighting based on covariates associated with the chance of censoring, with G-computation, a sophisticated method of standardization, and with a joint model for the survival and censoring processes. For the numerator, the denominator, and the cost effectiveness ratio as a whole, G-computation gave the smallest bias. This method is technically feasible and transparent for researchers familiar with multiple imputation techniques or simulation methods. The researchers recommend that this method is applied in cost effectiveness studies when the outcome concerns cumulative time-to-event, either in the base case analysis or as a sensitivity analysis. The G-computation method can however only be used to correct (nominator and denominator of) the ICER. The researchers do not mention how/whether this method can be used for the assessment of uncertainty (CEACs, NMB, EVPI). Therefore the usefulness of this method in its current form seems to be limited. Further research could focus on the use of the method for uncertainty assessment.

Guideline 9: Discounting

Project	Topic	Recommendation
152002008	Discounting	REVISION

Project 152002008 investigated discounting. As the researchers of the project state: Already in the pilot a trend became clear showing a decreasing discount rate with increasing time horizon, for example, potentially supporting hyperbolic discounting instead of the traditional constant discounting procedure. Consequently, with the traditional approach health gains in the future might still be undervalued despite the use of differential discounting in, for example, the Netherlands and Belgium. Furthermore, it was found that discount rates differ for health and money, supporting the differential discounting approach. The difference found between quality of life versus life years in this respect might even support considering a 3-dimensional instead of the traditional 2-dimensional approach. Further research (including the large scale study in progress) would be needed to confirm these results, before new recommendation and/or revision of the guidelines.In the guideline differentiation of discount rates (into 3 or 4 dimensions) might be considered (possibly after further research, as confirmation of the findings of the pilot study seem indicated. In addition, studies to assess the impact of using hyperbolic rather than constant discounting in health economic evaluation seem indicated.

Guideline 10: Uncertainty analysis

Project	Topic	Recommendation
152002001	Bayesian analysis	REVISION
152002005	Value of information	REVISION & RESEARCH
152002006	Meta analysis and Value of Information	REVISION & RESEARCH
152002007	Framing a health technology assessment	REVISION
152002021	Heterogeneity	REVISION & RESEARCH

Project 152002001 is described under guideline 7.

Project 152002005 studied the importance of value of information analysis, specifically when considering conditional reimbursement, as a tool to a) make sure that all relevant data gets collected during the study period so that the CEA enables a final decision about reimbursement, and b) make sure no resources are wasted on new research that will not contribute to the ability to make a final decision. The researchers conclude that the probabilistic sensitivity analysis and expected value of perfect information analyses should always be performed to determine whether further research might be worthwhile. Expected value of perfect parameter information and expected value of sampling information may not always be necessary. They developed a flow diagram to decide what analyses should be performed to identify the need for additional research. The researchers planned to test the flow diagram on 4 real-life models, but 2 of those were not available in time. The two real-life models that were used showed results in the same direction, which, in the words of the researchers themselves ‘gives confidence in the generalizability of our conclusions’. However, as ZonMw commented, validation of the results in other case studies seems indicated. The researchers specifically do their recommendations in the case of conditional

reimbursement. However, this may be an unnecessary limitation, as the flow diagram could apply to all economic evaluations with value of information analyses.

Project 152002017 is described under guideline 7.

Project 152002007[2] developed a checklist to systematically frame health technology assessments for resource allocation decisions in a way that they are applicable to the decision problem. The checklist consists of eleven factors: objective, audience, perspective, population, comparators, clinical practice, time horizon, consequences, patient use, professional use, and price and resource use. The project results indicated that incorporating parameters that improve the applicability of health technology assessments was feasible and had considerable impact on the assessment of uncertainty. The checklist may be useful to frame a health economic evaluation, and to determine the steps in reducing uncertainty around certain strategies using value of information analyses.

Project 152002021 is described under guideline 7.

4.2.2 Guideline outcome research

HTA METHODOLOGY PROJECTS

The large majority of HTA methodology projects that applied to the guideline outcome research are already described in the previous paragraph. Project 1520012012 explored the feasibility and qualifications of a cancer registry to be usable for estimating (cost-)effectiveness of oncological drugs. Another project (152002017) investigated the use of several correction techniques for confounding bias in economic evaluations based on observational data. Two projects (152002025, 152002026) focused on methodology to assess clinical effectiveness specifically. These projects do not apply to the pharmaco-economic guideline, but do apply to a chapter in the guideline outcome research. See Table 5 for an overview of the 28 HTA methodology projects in relation to the guideline outcome research and reference to the chapter in the pharmaco-economic guideline, if applicable.

Project 1520012012 (NO REVISION NOR RESEARCH) explored feasibility and qualifications of a dedicated cancer registry like the Eindhoven Cancer Registry (ECR) to be usable for estimating (cost-)effectiveness of oncological drugs, concurrent with the requirements by the Dutch policy for reimbursement of new, often expensive, anti-cancer drugs. In order to judge feasibility, the degree of upgrade and expansion of the data collection was investigated. In addition, the value of linkage with an external database (PHARMO) was evaluated. The researchers concluded that: 1) the expansion of the dataset of the ECR with data concerning distant recurrences was feasible, and 2) The linkage of a cancer registry with other databases such as a hospital pharmacy/public pharmacy database such as Pharmo was feasible (in the Netherlands), provided valuable data for HTA research and alternatives to the expansion of cancer registries. This project showed the possibility to link disease specific registries with pharmaceutical registrations, which reflect the use of health care resources.

[2] See also description of this project under guideline 1

Table 5 HTA methodology projects in relation to the guideline outcome research

Guideline Outcome research / Project	**Topic**	**See pharmaco-economic guideline:**
Guideline 2: Modeling versus trial		
152002001	Bayesian analysis	7,10
152002002	Meta-analysis	7
152002005	Value of information	10
152002006	Meta-analysis and VOI	7, 10
152002007	Framing a health technology assessment	1 to 7, 10
152002008	Discounting	9
200400002	Modeling behavior	7
Guideline 3: Costs		
152002003	Spill-over effects: Informal care	5
152002007	Framing a health technology assessment	1 to 7, 10
152002009	Spill-over effects: informal caregivers	6
94506414/E&K	Cost measurement	5
152002018	Productivity costs	5
152002022	Indirect medical costs	5
Guideline 4: Patient characteristics, clinical outcome		
152002007	Framing a health technology assessment	1 to 7, 10
152002027	Censoring	8
1708856019/E&K	Evaluative space: patient effects of testing	6
152002026	Predictive markers in RCTs	Not applicable
Guideline 5: Patient reported outcomes		
152002007	Framing a health technology assessment	1 to 7, 10
152002009	Spill-over effects: informal caregivers	6
152002010	Time preferences in time trade off	6
152002013	Utility mapping	6
152002015	Utility mapping	6
152002020	Momentary experienced utility	6
152002023	Spill over effects: significant others	6
94506257/E&K	Evaluative space: outcomes beyond health	6
945077039/E&K	Proxy measurement	6
Guideline 6: Clinical practice		
152002007	Framing a health technology assessment	1 to 7, 10
152002017	Confounding bias	Not applicable
152002025	Generalisability and extrapolation of trial data	Not applicable
1708830019/IMP	Long run - short run efficiency paradox	4
Guideline 7: Action plan for outcome research		
152002005	Value of information	10
152002012	Use of registries	Not applicable.
152002021	Heterogeneity	7,10

Project 152002017 (REVISION & RESEARCH) investigated the use of several correction techniques for confounding bias in economic evaluations based on observational data. The methods under investigation were propensity score matching, propensity-score-as-covariate

regression, inverse probability weighting and instrumental variable regression. Several different specifications of these methods were tested. A simulated dataset of patients with colorectal carcinoma was used in order to assess the results of the different adjustment techniques. The researchers state the following recommendations: Adjusting for confounding bias is most likely to be successful when the association of treatment and confounders is addressed, instead of the association of outcome and confounders. After estimating propensity scores in order to achieve covariate balance across treatment groups, the model estimating the outcome should be kept as simple as possible. This reduces the risk of misspecification of the functional form or the link function. Inverse probability weighting and propensity-score-as-covariate regression are preferred because they provide estimates with narrower confidence intervals than one-to-one propensity score matching. Also, they developed a decision support tool that provides guidance for the selection of the most appropriate method for bias reduction for their research on 'real world' data regarding cost-effectiveness analysis based on observational studies. In the guideline outcome research a more detailed recommendation could be made on which statistical correction technique could be used in which situations. The decision support tool developed by the authors could be included in the guideline. At the same time, further research in the performance of the techniques in different situations seems indicated. Specific directions for this research could be informed by a systematic review of relevant literature on this topic.

Project 152002025 (REVISION & RESEARCH) investigated the generalizability of pragmatic trials, the extrapolation of efficacy found in pragmatic trials to daily practice, and the impact of generalizability and extrapolation on cost-effectiveness in rheumatoid arthritis (RA). The results of the project indicated that characteristics of patients included in pragmatic RCTs and also treatment effects found in pragmatic RCTs can be substantially different from clinical practice. Prognostic factors possibly impact treatment effect. Because treatment effect is an important part of cost-effectiveness, this finding is relevant for economic evaluations. The researchers advise that in the interpretation of results of phase II/III clinical trials in RA, the prognostic factors and co-treatment need to be explicitly taken into account. For this interpretation, prediction models as developed in the present study can be a starting point. Furthermore, they propose to always do sensitivity analyses with respect to the treatment effect from published (pragmatic) trials/RCTs as used in the cost-effectiveness analysis, for instance by using the developed prediction models (in case of RA).The revisions to the guidelines the authors suggest, seem preliminary given the fact that this project was only performed in patients with RA, and the prediction model is not yet validated. Further research is needed to validate the prediction model. In addition, as the results from this research only apply to RA the same procedure should be repeated in a number of other diseases to check whether the conclusions hold. This would however involve a substantial amount of research.

Project 152002026 (REVISION) aimed to develop a strategy for including evaluations of potentially predictive markers in the design phase of pharmaceutical trials. In general, trials are designed to evaluate the effects of treatment at the group level, and conclusions and decisions about pharmaceuticals apply to this group as a whole. In reality, there could be substantial and relevant between subgroup heterogeneity in the effects of treatment. Predictive markers are biomarkers that are associated with a differential response to treatment. If the association is confirmed, they could be used to target treatment: toxic or

expensive pharmaceuticals or other interventions are administered to marker positive patients only, while marker negative patients receive a different intervention. In the last few years a number of interesting study designs and analytic strategies have been proposed to evaluate the value of predictive markers in phase III clinical effectiveness trials. It was however unclear what the relative effectiveness and efficiency of these strategies was. In this project, the authors developed a guidance document for the evaluation of putative predictive markers in randomized clinical trials and discussed analytic strategies, including sequential and adaptive on. The strategy was based on an extensive literature search, a series of simulations, and additional analyses of completed and on-going drug and intervention trials in the ZonMw effectiveness program. The researchers describe a number of considerations that can be used to select from study designs, to evaluate the effects of using one or more markers as predictive markers (treatment selection markers). For this purpose a guidance document was developed. In registries / outcome research treatment selection biomarker could be registered and can be used as patients' characteristics.
In the guideline it could be mentioned that, when biomarkers are used, the guidance document should be followed.

T=4 DOSSIERS

Dossiers	Orphan drug?	Recommendation
Bortezomib (Velcade) bortezomib for myeloom and oxaliplatin for coloncarcinoma (pilot study)	No	REVISION AND RESEARCH
Omalizumab (Xolair) for asthma	No	REVISION AND RESEARCH
Ranibizumab (Lucentis) for macula degeneration	No	REVISION AND RESEARCH
Agalsidase alpha (Replagal) and agalsidase beta (Fabrazyme) for Fabry's Disease	Yes	REVISION AND RESEARCH
Alglucosidase alpha (Myozyme) for Pompe's Disease	Yes	REVISION AND RESEARCH

The aims of the pilot study on Bortezomib (Velcade) and oxaliplatin were: 1) to obtain experience with designing and executing outcomes research; 2) to generate knowledge with respect to methodological issues associated with dynamics in daily clinical practice; and 3) to examine the feasibility to obtain valid and precise incremental cost-effectiveness estimates. For this purpose two T=4 dossiers (bortezomib for treatment of relapsed or refractory multiple myeloma and oxaliplatin for stage III and IV colorectal cancer) were considered. It was concluded that it was feasible for an outcomes research study to provide relevant information about appropriate drug use (who gets it, and what do they receive) as well as the diffusion of the drug and the dynamics of treatment in daily practice. However, to use outcomes research in an optimal way the researchers list a number of critical success factors: appropriate research design available at T=0, clearly defined research questions aiming to revealing and/or reducing uncertainty at reappraisal, collaboration between regulatory agency, medical field and HTA agencies, flexibility and customisation. They also mention a number of drawbacks of outcome research: financial and time investments, observational studies have important bias and confounding issues, data availability, dynamics in daily practice. Specific recommendations by the researchers are the following:

a. Choice of research design should depend on type of disease, type of drug and expected dynamics in daily practice
b. Appropriate time frame depends on type of disease and drug
c. Disease specific registries can help to obtain sufficient numbers of similarly treated patients and enable uniform response criteria, support data collection and thereby facilitate outcomes research.
d. Real-world evidence development on appropriate use should reveal who receives the drugs and how the drug is given in daily practice
    i. Insight into who receives the drug requires a minimal real-world dataset
    ii. Insight into how the drug is given requires a detailed real-world dataset
e. Flexibility is needed regarding the objectives and subsequent requirements of outcomes research; it is necessary to accept flexibility in study characteristics, including the evidence development time frame and the questions that outcomes research should answer.
f. Where appropriate, cost-effectiveness estimates should be based on a synthesis of real-world data and other evidence (e.g. evidence from randomised controlled trials) in order to obtain a valid and precise incremental cost-effectiveness measure.
g. The study plan should include a clear statement of how the data collection will reduce uncertainty for decision makers at the reappraisal time. Early modelling and/or value of information analysis can assist in the identification of important knowledge gaps.

These success factors, drawbacks and recommendations could be incorporated in the Guideline Outcomes Research, chapter 7: Action plan for outcome research.

Beyond this pilot study, over the past years, there is a significant and growing interest among both the payers and producers of medical products for risk sharing agreements such as coverage with evidence development as currently applied under the Dutch 'expensive medicines' policy regulation. These risk-sharing agreements often concern a specified period of time wherein a medical product is temporarily reimbursed while collecting evidence to resolve (a part of) available decision uncertainty. The (future) price and utilization of the product depends on the outcomes achieved during this period. Through this dependence on the outcomes achieved, these 'performance-based' risk-sharing agreements may lead to value based pricing.It is worth noting that next to coverage with evidence development, other risk-sharing agreements exist. This includes ex ante reimbursement schemes wherein the treatment is only reimbursed for pre-selected individual patients and ex post reimbursement wherein treatments are only (fully) reimbursed or continued dependent on treatment response or intermediate outcome. The role of other risk-sharing agreements next to coverage with evidence development could be explored.

Additional topics for further research could be:

- A decision framework for initiating outcomes research or risk-sharing agreements. It would be valuable to extend the "Stroomschema voor een pragmatische opzet van het uitkomstenonderzoek" with a framework to decide whether it would be valuable to initiate outcomes research. This framework might consider questions such as 'what decision uncertainty is present' and 'which research could be used to address this decision uncertainty', and 'is this research feasible and valuable'. Many of the gaps and uncertainties in existing evidence, while interesting to resolve, are unlikely

to reduce decision uncertainty once resolved through outcomes research (the ultimate goal of initiating outcomes research). If the decision uncertainty cannot be resolved using feasible research options, or is not valuable (EVSI) then the value of initiating additional outcomes research should be questioned. Additionally, different risk-sharing agreements might be considered as well in the updated framework (see also heading “4) Role of other risk-sharing agreements” in this section).

- Synthesis of real-world data and other evidence.
  Although it may be valuable to collect real-world data on costs and effects in specific cases, it is unclear how these data should be combined with other evidence (e.g. evidence from randomised controlled trials). Evidence obtained from (randomised) trials is likely to present treatment efficacy, while evidence obtained from real-world data is likely to present treatment effectiveness. Simply synthesizing these two sources together could be inconsistent. It is unclear whether and how these two types of data should be combined or whether they should be handled separately. In case of presenting separate analyses for trial data and real-world data, it becomes challenging to draw firm conclusions or formulate guidance if these separate analyses are conflicting in terms of effectiveness and/or cost-effectiveness.

- Evaluation based on pilot studies containing both T=0 and T=4 assessments
  The presented pilot outcomes research resulted in important success factors, drawbacks and recommendations for outcomes research during the coverage with evidence development period. However, as no T0 measurement was available in the pilot considered, the degree that these pilot studies achieved their main goal (reducing available decision uncertainty) was not evaluated. Therefore, in a future evaluation it would be valuable to compare T0 and T3 assessments and assess the reduction in existing decision uncertainty. Additionally, both pilot studies applied a retrospective design for pragmatic reasons (i.e. time restrictions) in contrast with recommendations from Guidance for Outcomes Research (‘Leidraad voor Uitkomstenonderzoek’). Retrospective data collection could be performed at T=0, while prospective data collection would require the temporary reimbursement period. A future evaluation of the coverage under evidence development scheme could assess the feasibility and role of prospective studies within the time period to formulate recommendations for initiating prospective studies.

- Role of other risk-sharing agreements next to coverage with evidence development
  As discussed above in the section ‘Recent developments in relation to the project’, next to coverage with evidence development other risk-sharing agreements exist and are increasingly being used. These performance linked reimbursement schemes can be considered to manage the real-world utilization of medical products while collecting evidence. Further research should focus on how the different options relate to each other and how to select the most appropriate option in a specific situation.

- Resolving decision uncertainty through acknowledging patient heterogeneity
  The ultimate goal of outcomes research during the coverage with evidence development period is to reduce decision uncertainty. This decision uncertainty may originate 1) because we do not know the exact input parameters / variables in an

economic evaluation (parameter uncertainty) and 2) due to genuine differences between patients (natural variation / variability) that can in part be explained by patient characteristics (patient heterogeneity). When aiming to reduce decision uncertainty, the focus is often primarily on reducing parameter uncertainty. However, acknowledging patient heterogeneity may also resolve decision uncertainty and at the same time increasing net health benefits (2, 3). Especially when there are large dynamics in daily practice, acknowledging patient heterogeneity might be valuable. Therefore, the role of examining patient heterogeneity next to parameter uncertainty during the coverage with evidence development period could be considered.

The two additional dossiers on expensive medicines (Xolair and Lucentis) provided further insight in the process and outcomes of conditional reimbursement / outcome research for expensive drugs, and confirmed the findings of the above described pilot study.

Furthermore, the two dossiers that concerned orphan drugs (Replagal and Myozyme) revealed some issues that are specific for the assessment of the (cost-)effectiveness of and decision making on these types of drugs. Issues that were most apparent are the following:

- It is questioned whether the conventional threshold of (around) 80.000 euro per QALY gained should be used for therapies for orphan diseases. Also, it is unclear how the cost-effectiveness results should be weighted against other aspects such as necessity, feasibility, rarity, severity, and ethical considerations.
- Taking into account the generally high incremental cost-effectiveness ratios at T0 (indicating low decision uncertainty), and the relatively small impact outcome research is likely to have (due to the small patient numbers), the value of initiating outcomes research is open for debate.
- The role of other risk-sharing agreements next to coverage with evidence development can be considered. Further research should focus on how the different risk-sharing agreements relate to each other and how to select the most appropriate option in a specific situation.

4.2.3 Manual cost research

Ten HTA methodology projects were found to apply to the Manual cost research. All ten projects also applied to the pharmaco-economic guideline. See Table 6 for an overview.

Table 6 HTA methodology projects in relation to the Manual cost research

Manuel cost research / Project	**Topic**	**Discussed in: Guideline**	**Number**
Chapter 3: Action plan for cost research			
152002007	Framing a health technology assessment	Pharmaco-economic	1
Chapter 4: Direct health care costs			
152002017	Confounding bias	Outcome research	6
94506414/E&K	Cost measurement	Pharmaco-economic	5
Chapter 5: Direct costs outside health care			
152002009	Spill-over effects: informal caregivers	Pharmaco-economic	6
152002017	Confounding bias	Outcome research	6
152002023	Spill over effects: significant others	Pharmaco-economic	6
152002003	Spill-over effects: informal care	Pharmaco-economic	5
Chapter 6: Indirect costs outside health care			
152002017	Confounding bias	Pharmaco-economic	5
152002018	Productivity costs	Pharmaco-economic	5
152002023	Spill-over effects: significant others	Pharmaco-economic	6
94506414/E&K	Cost measurement		
Chapter 7: Indirect health care costs			
152002022	Indirect medical costs	Pharmaco-economic	5
Chapter 8: Special considerations			
152002008	Discounting	Pharmaco-economic	9
1708830019/IMP	Long run - short run efficiency paradox	Pharmaco-economic	4

A special note should be made with respect to the projects that investigated the inclusion of spill-over effects in caregivers (152002003, 152002009) or significant others in general (152002023). The inclusion of these (potentially highly relevant) effects on the effect side of the ICER introduces a risk of double counting if (parts of the) spill-over effects are also included on the cost side of the ICER, not yet specified in the cost manual.

5. CONCLUSIONS AND DISCUSSION

General findings

The 36 HTA methodology projects considered in this report covered a broad range of methodological topics. Thus far (April 2013), a total of 47 publications, 17 publications in preparation and 39 presentations can be considered output of the HTA methodology projects. The output is likely to increase, as a large proportion of the projects was finished only recently. The projects funded in the Expensive medicines and orphan drugs program relatively more often delivered instruments (models, questionnaires, frameworks, checklists, etcetera) than the other two programmes. Not all projects applied to the guidelines. Five projects were not considered methodological projects, but merely applications of methods. Four projects did not relate to a chapter in the pharmaco-economic guideline. Of these projects, two projects focused on clinical effectiveness, one project investigated the use of registries for economic evaluation, and one project investigated confounding bias. These four projects did relate to the guideline outcome research. Three projects did not relate to any of the guideline documents (two projects on equity and one project on implementation). In conclusion, the large majority of projects had a direct link with one or more of the existing guideline documents. The majority of the project results indicated revision, or further research, or both.

Several limitations of this research must be listed. First of all, the limited time available hampered a systematic review on the topics of the projects. Instead, a scoping review was performed. As a result, it cannot be ruled out that potentially relevant information has been missed, that could change the decision and/or direction for further research and/or revision. Second, the research provides an overview of the tangible output of the projects as well as the potential relevance of the project for guideline revision and/or further research. As such, it is NOT a full evaluation of the value and impact of HTA methodology research funding, and should not be regarded as such. HTA methdology research has broader benefits, such as the ability to maintain a critical research capacity for HTA research groups, the improvement of teaching activities, the support of the scientific careers of PhD researchers, post docs as well as senior researchers, the international position of Dutch HTA methodology research, and (probably) more. A third limitation is the inherently subjective decision whether the results of a project indeed are relevant and/or mature enough to indicate revision of the guideline. Likewise, the indication of areas for further research is a subjective statement. The research procedure (two researchers per project, plenary discussions of each project in the project team) was however designed to minimize this. Nevertheless, it must be emphasized that the results do not reflect decisions, but merely aim to provide indications for revision and/or research and inform further discussion based on this document. This is because researchers often do not clearly state, and argue, whether the results of their project warrant revision of the guideline and or further research. Many researchers answer the question in the ZonMw end report form with a simple ‘yes’ or ‘no’. The key outcomes are listed in Box 1

Box 1 Key outcomes

Project topics for which results *only* indicated revision of the guidelines:

- methodology for the assessment of clinical effectiveness (not in the guideline),
- framing of an economic evaluation (not explicitly mentioned in the guideline),
- long run - short run efficiency paradox (guideline 4),
- discounting (pharmacoeconomic guideline 9: discounting),
- place and value of Bayesian analysis (guidelines 7 & 10).

Project topics for which results *only* indicated research:

- proxy measurement (guideline 6),
- spill-over effects to persons to children (guideline 6),
- patient perspective (guideline 6).

Project topics for wich results indicated both revision of the guidelines and research:

- broadening the evaluative space to aspects other than health (guideline 6),
- the place and value of patient preferences (guideline 6),
- double counting issues related to the incorporation of spill-over effects in informal caregivers and significant others (guideline 5 & 6),
- utility mapping: specific instruments to generic preference based instruments (guideline 6),
- uncertainty: Bayesian analysis, meta-analysis, value of information analysis, acknowledging heterogeneity (guideline 10 + outcome research),
- indirect medical costs (guideline 5).

Recommendations for research

For the purpose of the prioritization of research topics, the results of this project should be considered in relation to the 28 HTA methodology projects that are currently underway. See Table 7.

With regard to three topics for which further research seemed indicated based on the findings of the HTA methodology projects that are finished, related projects are currently underway: the evaluative space, patient preferences, and uncertainty.

- The topic ‘ evaluative space’ is concerned with the question what is considered as the measure of benefit in health economic evaluation. Is it health (related quality of life) or are other aspects also important? In this light, the on-going project 152002023 is relevant, in which an instrument to measure well-being is being developed and validated. Also relevant is the program ‘ Quality of life and health’ (KVLG) of NWO/ZonMw that is currently in process. This program asks for a collaboration between experts from philosophy and health care in order to investigate the conceptualisation and measurement of quality of life in several populations. A different conceptualisation of benefit in health economic evaluation may warrant a different measurement approach.

Table 7 Overview of HTA methodology projects currently underway

Project	Title	End
ZonMw Theme: Decision making		
152002031	Real options to support decision making on reimbursement of new drugs	01-09-12
152002038	When is it too expensive?	01-03-13
152002041	Incorporating age-dependent reference points in health technology assessment	01-09-13
152002045	HTA guidelines to assist in the decision making process for the reimbursement of orphan drugs	01-01-14
152002046	Integrating evidence on patient preferences in health care policy decisions: are we up for it?	01-01-14
152002048	Risks of conditional reimbursement: stopping can be more difficult than not starting!	01-05-14
152002049	Are societal perspectives on resource allocation in health care reflected in recommendations and decisions about funding of costly end of life technologies?	01-10-14
152002050	Disease models used for decisions on expensive drugs: a new instrument to enable structured model assessment.	01-01-15
152002051	A roadmap for uncertainty analysis in MCDA	01-01-15
152002052	Taming uncertainty: Handling uncertainty in deciding upon new pharmaceuticals	01-11-14
152002053	Value judgment of (new) drugs in the Netherlands	01-09-14
ZonMw Theme: Design & analysis		
152002029	Combining N-of-1 trials to estimate population clinical and cost-effectiveness of drugs using Bayesian hierarchical modeling.	01-01-13
152002030	From rationing to rationality: an n-of-one trial service for off-label medicines	01-11-12
152002034	States worse than dead: measurement, estimation, and interpretation	01-04-13
152002035	Optimal design and analysis for clinical trials in orphan diseases	01-10-12
152002036	Developing structural marginal models for the analysis of time-dependent drug use in observational studies	15-06-13
152002040	Obtaining causal effect parameters from large databases using physician's preference as instrumental variable	15-01-14
152002047	Multiple imputation and bootstrapping in health economic data	01-11-14
ZonMw Theme: Costs & outcomes		
152002024	Quantifying health status in dementia	01-02-13
152002028	Patient preferences for and experiences with chronic medication use: development of two web-based instruments	01-03-13
152002032	Valuation of patient time	01-09-12
152002033	Measuring the effects of health interventions on subjective well-being: SWB-xD	01-08-13
152002037	Web-based time trade-off incorporating interviewer help: Efficiency with validity	01-07-13
152002039	Test of lead time TTO in the general population	01-12-12
152002042	What is best when using drugs in chronic disease?	01-09-13
152002043	Establishing reference prices from the national database of the DBC system	01-01-14
152002044	A Dutch tariff for the EQ-5D-5L	01-04-13
152002016	The marginal utility of health: direct and indirect valuation of EQ5D differences	01-06-12

- The place and value of patient preferences: This topic is currently under investigation in project 152002046. In addition, one project currently investigates patient preferences related to medication use (152002028). The topic is also related to the previous one regarding 'evaluative space', as patients' preferences may regard issues besides health alone.

- Uncertainty is currently under investigation in several projects: real options analysis (152002031), uncertainty in MCDA (152002051), handling uncertainty in decision making (152002052), and multiple imputation and bootstrapping (152002047).

For the remaining topics for which further research seems indicated based on the findings of the HTA methodology projects that are finished no projects are currently underway:

- Patient perspective: Currently, societal preferences for health are used as outcome in health economic evaluations. New methods are being developed to measure patient experiences directly (such as the experience sampling method and the day reconstruction method). This may shed new light on the use of the patient perspective in health policy decisions as the results obtained using these instruments may be more valid than results obtained using retrospective or prospective measures. In addition, a different conceptualisation of benefit in health economic evaluation (described under the topic 'evaluative space') may warrant a different measurement approach. In this respect the new methods may also be of value.

- Spill-over effects to other persons: Especially, double counting issues related to the incorporation of spill-over effects in informal caregivers and significant others are still unsolved. In addition, the handling of spill-over effects to children is currently largely unclear. Research into these topics is important to improve assessment in situations in which spill-over effects to other persons are influential (e.g. impact on the incremental costs and effects). Apart from the double counting issue, questions remain with regard to the integration if spill-over effects in economic evaluations.

- Utility mapping of specific instruments to generic preference based instruments: This is an increasingly important topic as in many clinical trials utilities are not directly obtained from the patients, and mapping from specific instruments to utilities proves difficult. An overview and quality assessment of mapping algorithms available could be valuable, as well as research to further improve the methodology of utility mapping.

- Proxy measurement: This is a topic for which information is available in the literature. A systematic overview and quality assessment of the types of proxy measurement available is however lacking.

- Indirect medical costs: For this topic two specific questions were formulated. First, if indirect medical costs will be incorporated, it still remains unclear how *non*-medical indirect costs should be considered. Second, much focus is now directed at estimation of indirect medical costs and surrounding uncertainty. It can be argued that estimation of long term QALYs in decision models should be handled with the same scrutiny.

Recommendations for guidance

In the process of conducting this research, it became apparent the guideline documents (pharmaco-economic, outcome research, and costs) are not fully consistent. This could result in inconsistencies in the practice of performing economic evaluations. Ideally, the guidelines would consist of a single document, which incorporates all existing guidance in an unequivocal way. In addition, the level of detail differs considerable from chapter to chapter and topic to topic in the guideline documents. Some sections of the guideline documents make an explicit reference to the use of specific outcomes or instruments, whereas other sections are generally described and offer no practical guidance. In this respect, the guidelines could be more balanced.

Two topics are currently not (explicitly) considered in the guidance documents: methodology for the assessment of clinical effectiveness and framing of an economic evaluation. As both topics are crucial parts of an economic evaluation, it seems indicated to include chapters on these topics in the guideline. The HTA methodology project results, as well as other literature, may inform these chapters.

For two topics it seems indicated to simply solve the discrepancy that exists between the different guidance documents: long run - short run efficiency paradox (pharmaco-economic guideline 4), indirect medical costs (guideline 5).

Six topics relate to guideline 6 in the pharmaco-economic guideline: broadening the evaluative space, the place and value of patient preferences, patient perspective, spill-over effects, utility mapping and proxy measurement. For the latter two, an overview and quality assessment of available information would be valuable to inform the revision of the guideline on these topics. The remaining four topics are somewhat intertwined. All four relate to fundamental considerations with regard to health economic evaluations: What constitutes benefit and in whom to measure and value? Any position in this matter is likely to influence outcomes of assessments considerably. As the choice for a position is essentially normative, a broad discussion on these topics seems valuable. At the same time, an abundance of empirical information on these topics is available, and revision may benefit from a systematic overview of what is known. The guideline could be more explicit on

- the place and value of outcomes broader than health, such as well-being for instance,
- the place and value of the patient perspective compared to the societal perspective with regard to health,
- the place and value of patient preferences for health care (research is underway – 152002046),
- when to incorporate spill-over effects to other persons than the patient, and how to present / integrate outcomes in other persons to decision makers.

Guideline 9 (Discounting) in the pharmaco-economic guideline could be revised according to the results of project 152002008.

Guideline 10 (Uncertainty analysis) in the pharmaco-economic guideline could be updated with information from the HTA methodology reports and the literature. This may include information on Bayesian analysis, meta-analysis and heterogeneity. Noteworthy is that a

number of projects on uncertainty are currently underway: real options analysis (152002031), uncertainty in MCDA (152002051), handling uncertainty in decision making (152002052), and multiple imputation and bootstrapping (152002047). It might be advisable to postpone revision, or parts of the revision, until the results of these projects are available.

With regard to the guideline outcome research, the projects on the subject of value of information are specifically relevant. ZonMw invited the project leaders of the HTA methodology projects on this subject (152002005, 12002006, 152002007, 152002031) to do a proposition for a valorisation and implementation grant (VIMP). The goal of this grant is to write a chapter on value of information for the guideline outcome research. In addition the ongoing HTA methodology projects on orphan drugs (152002048), conditional reimbursement (152002048), and uncertainty (152002052) are likely to be relevant for the guideline outcome research as well.

APPENDIX: Overview of projects

1	152002001	Design & Analysis	Prof. G.J. van der Wilt / UMC St. Radboud	Potential and limitations of a Bayesian approach to the analysis and synthesis of evidence from multiple, heterogeneous sources. An inquiry into its usefulness in supporting policy decisions on drugs
2	152002002	Design & Analysis	Dr. M.P.M.H. Rutten-van Mölken / EUR	Updating parameters of decision-analytic cost effectiveness models: A sytematic comparison of methods
3	152002003	Costs & Outcomes	Dr. M.E. van den Akker / LUMC	Further exploration of the appropriateness of the well-being valuation method for monetary valuation of informal care: what is measured?
4	152002004	Design & Analysis	Dr. K. Fischer / UMC Utrecht	Treatment of severe hemophilia: Optimal data-usage for optimal treatment strategies
5	152002005	Decision making	Dr. M.J. Al / EUR	Prioritizing and designing outcomes research: the role of value of information analysis
6	152002006	Decision making	Prof. dr. M.J. Postma / RUG	Bayesian Value of Information and Indirect Comparison Methodologies Applied to Dutch Expensive In-hospital Drugs: optimizing information gathering and synthesis illustrated for anti-fungal drugs
7	152002007	Decision making	Dr. M.A. Joore / MUMC+	A framework for real world economic evaluation of pharmaceuticals
8	152002008	Design & Analysis	Prof. dr. M.J. Postma / RUG	Discounting Health Effects; further analysis of its rationale and the theoretical & empirical implications
9	152002009	Costs & Outcomes	Prof. dr. W.B.F. Brouwer / Erasmus MC	The inclusion of informal care in health economic evaluations: developing a standardised, modular instrument and user manual including the CarerQol
10	152002010	Design & Analysis	Prof. dr. W.B.F. Brouwer / Erasmus MC	Correcting health state valuations derived with TTO for discounting
11	152002011	Decision making	Prof. dr. W.B.F. Brouwer / Erasmus MC	Equity weights for QALYs
12	152002012	Costs & Outcomes	Prof. dr. J.W.W. Coebergh / IKZ	Feasibility of cancer registries as a Health Technology Assessment tool in pharmacotherapy
13	152002013	Costs & Outcomes	Dr. E.A. Stolk / EUR	Quality of life in expensive drugs: deriving preferences in absence of generic health state valuations

14	152002015	Costs & Outcomes	Prof. dr. C.A. Uyl-de Groot / EUR	From disease specific health status to generic utility. Methods to improve piggy-back utility analysis in controlled clinical trials
15	152002017	Design & Analysis	Dr. W.K. Redekop / EUR	Confounding in real-life cost-effectiveness studies: assessing the validity and efficiency of different correction techniques
16	152002018	Costs & Outcomes	Dr. L. Hakkaart-van Roijen / EUR	Productivity costs in cost-effectiveness studies on expensive drugs
17	152002019	Decision making	Dr. M.E. van den Akker / LUMC	Societal preferences for basic health insurance in the Netherlands
18	152002020	Costs & Outcomes	Dr. M.A. Joore / MUMC+	The Q in the QALY: exploring new methods
19	152002021	Design & Analysis	Dr. J.P.C. Grutters / MUMC+	Acknowledging heterogeneity in Health Technology Assessment to improve efficient use of pharmaceuticals
20	152002022	Costs & Outcomes	Dr. P.H.M. van Baal / EUR	Estimating indirect medical costs and its associated uncertainty
21	152002023	Costs & Outcomes	Prof. dr. W.B.F. Brouwer / EUR	Significant others in economic evaluations
22	152002025	Design & Analysis	Dr. P.M.J. Welsing / UMCU	A new modelling approach combining effectiveness data from randomized trials and observational studies in (cost-) effectiveness analyses in rheumatoid arthritis. Reconciling two paradigms
23	152002026	Design & Analysis	Prof. dr. P.M.M. Bossuyt / AMC	Evaluating predictive markers in randomized clinical trials of pharmaceuticals
24	152002027	Design & Analysis	Dr.ir. M.J.C. Eijkemans / UMCU	Informative censoring in time-to-event data and consequent bias in HTA
24	94504558/E&K	Costs & Outcomes	Prof.dr. G.J. Bonsel / AMC	When outcome is a balance. Methods to measure combined utility in obstetrics. Additional study to study 556-558;560-563 all involving choosing between active treatment (ususally including cesarean section) and watchful waiting, or a analogue dilemma
26	94514010/IMP	Costs & Outcomes	Drs. W.J. Meerding / EMCR	Patients' and general practitioners' preferences for osteoporosis treatment ancillary study of 'Case finding in Osteoporosis: how to implement current guidelines?'
27	94514411/IMP	Costs & Outcomes	Dr. C.D. Dirksen / AZM	Investigating the added value of conjoint analysis for the evaluation of barriers and facilitators in implementation studies: the case of breast cancer surgery in ultra-short stay
28	94506257/E&K	Costs & Outcomes	Dr. M.A. Joore / MUMC+	Outcomes beyond health

29	94506414/E&K	Costs & Outcomes	Dr. L. Hakkaart-van Roijen / EMCR	Validation of the 'Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness' (TiC-P) for measuring health care utilisation and production loss
30	94516309/IMP	Design & Analysis	Dr. E. Buskens / UMCU	Predicting efficient implementation and costs; Ultrasound screening for developmental dysplasia of the hip
31	945077039/E&K	Costs & Outcomes	Dr. P.F.M. Krabbe / UMCN	Proxy HRQL value measurement in Alzheimer's dementia
32	945077309/E&K	Costs & Outcomes	Dr. M.P.M.H. Rutten-van Mölken / EMCR	Quantifying COPD patients preferences for early assisted discharge and inpatient hospital care for COPD exacerbations: a Discrete Choice Experiment
33	1708856019/E&K	Design & Analysis	Dr. B.C. Opmeer / AMC	The value of information in the evaluation of diagnostic and screening tests
34	1708830019/IMP	Design & Analysis	Dr. E.M.M. Adang / UMCN St Radboud	The long run - short run efficiency paradox in health care
35	1709925039/E&K	Design & Analysis	Prof. dr. E.W. Steyerberg / Erasmus MC	Dynamic updating of prediction rules in a computerized decision support system
36	200400002	Design & Analysis	Universiteit Twente, Dr. M.E. Pieterse	From intermediate outcomes to physical endpoints of behavioral change: modeling cognitive parameters for cost-effectiveness analyses in health promotion