Evaluation Health Technology Assessment Methodology Programme

Programma
Goed Gebruik Geneesmiddelen

ZonMw

Health Technology Assessment Methodology Programme

Review of External Evaluation Committee

Health Technology Assessment Methodology Programme

Review of the External Evaluation Committee

October 2015

Colophon

ZonMw is The Netherlands Organisation for Health Research and Development

Progress requires research and development. ZonMw funds health research and stimulates use of the knowledge developed to help improve health and healthcare.

ZonMw's main commissioning organisations are the Ministry of Health, Welfare and Sport and the Netherlands Organisation for Scientific Research.

For further information on this publication or the programme, please contact Benien Vingerhoed through e-mail Farmacotherapie@zonmw.nl or by telephone +31 (0)70 349 53 29.

Authors: B. Jönsson, W. Oortwijn, F. Rutten, A. Wailoo
Date: October 2015

ZonMw
Laan van Nieuw Oost-Indië 334
2593 CE The Hague
P.O. Box 93245
2509 AE The Hague
The Netherlands
Phone +31 (0)70 349 51 11
Fax +31 (0)70 349 51 00
info@zonmw.nl
www.zonmw.eu

Content

Appendices

1 Introduction

In 2007, the Ministry of Health, Welfare and Sports (VWS) approved a research programme on expensive and orphan drugs with a total budget of approximately € 24 million. Part of this programme was focused on methodology development in the field of health technology assessment (HTA).

The goal of the HTA methodology programme was to develop and improve HTA methodology for application in drug efficiency research and decision-making on the efficient use and reimbursement of drugs. The programme had a budget of € 6.4 million and ran from August 2007 until 2015. The first projects were funded in 2008. Since the start of the programme, 53 projects have been funded across three selected themes (Cost & Outcomes, Decision-making, Design and Analysis). Of these 53 projects, 38 projects are finalized, 14 are on-going and 1 project was terminated.

In April 2015, ZonMw published an evaluation report of the HTA methodology programme. The self-evaluation covers the period August 2007-December 2014. The goal of the self-evaluation was to justify the programme budget to the Ministry of VWS. To review the self-evaluation report and to formulate recommendations for the future, ZonMw has installed an external committee in April 2015.

In this report, the external evaluation committee of the HTA methodology programme provides its conclusions and advice to ZonMw in accordance with its tasks.

1.1 External evaluation committee

The external evaluation committee consisted of four members: professor dr. Frans Rutten (chair), professor dr. Allan Wailoo, professor dr. Bengt Jönsson and dr. Wija Oortwijn (secretary). These are all international experts in the field of HTA and/or HTA methodology (see Appendix A for more information).

1.1.1 Tasks of the external evaluation committee

The main task of the external evaluation committee was to review the self-evaluation report taking into account whether the programme has been conducted according to the assignment by the Ministry of VWS. Furthermore, the external evaluation committee was asked to assess whether the conclusions and recommendations of the self-evaluation report are justified and may need further refinement.

The evaluation may be used as input for a possible new HTA methodology programme. Therefore the external evaluation committee was also asked to formulate lessons learned and to give advice regarding a potential new HTA methodology programme.

The (self-) evaluation of the programme by ZonMw will be send to the Ministry of VWS together with the report of the external committee.

1.1.2 Methods used by the external evaluation committee

The evaluation of the external committee took place in the period April 2015-September 2015. Due to the international character of the committee, it met only once in September 2015 to discuss the draft final evaluation report.

The external committee has used desk research and interviews with a selection of relevant stakeholders (see Appendix B) as main sources for this report. The secretary of the committee conducted telephone and face-to-face interviews with nine stakeholders as input for the evaluation. One stakeholder provided input by email. From each interview, a summary report was made and sent back to the interviewee for validation.

Before the interviews were conducted, the self-evaluation report of ZonMw was reviewed by the external evaluation committee members. The review led to additional requests for information about the actual results of the HTA methodology programme. As a response, ZonMw sent the following documents to the committee:

- Summaries of all funded projects of the HTA methodology programme;
- A report by Joore (2013) describing the usefulness of completed HTA projects[1] to update/revise HTA methodology guidelines by the National Health Care Institute (Zorginstituut Nederland - ZIN); and
- A report of a combined VIMP (Dissemination and Implementation Impulse) that includes the results of four projects on Value of Information (VOI) (Al et al, 2014). The VIMP on VOI led to a chapter on the use of VOI analysis that is included in the updated guideline on Outcome Research of ZIN. A VIMP is meant to facilitate additional communication and implementation activities enhancing the uptake of project results. The programme committee decides whether or not a project leader will be invited to submit a request for a VIMP, which is €50.000 at the maximum. ZonMw can also invite project leaders to submit a joint proposal, as was done in the case of VOI, which may result in a higher budget for the VIMP. In total, six VIMPs have been granted with a total budget of about €240.000.

The review of the self-evaluation report provided input for the interview guide (see Appendix C).The views and opinions of the stakeholders were important in helping the external evaluation committee to acquire a comprehensive and accurate view of the effectiveness of the programme and lessons to be learned for a potential future programme.

1.2 Layout of the report

In Chapter 2, we provide the review of the external evaluation committee with regard to the self-evaluation report. In Chapter 3 the views of external stakeholders on the current programme and a potential new HTA methodology programme are presented. In Chapter 4, we present the conclusions and recommendations for the future. In setting up a potential new HTA methodology programme, it would be beneficial to be aware of other initiatives in this area (see Appendix D).

[1] This includes 24 HTA projects funded within the HTA methodology programme that were completed before January 2013.

2 Review of self evaluation report

In this Chapter, we provide the views of the committee on the self-evaluation report (including additional information provided), without taking into account the views of the external stakeholders (these are presented in Chapter 3).

2.1 Performance of the HTA methodology programme

The independent review of the self-evaluation report of the ZonMw HTA methodology programme by the committee members showed great consistency.

The committee finds the evaluation report very clear and comprehensive in the way the programme is described. Overall, the evaluation conducted is a very well documented process review. The committee has the opinion that it would have been beneficial to include more information on the quality and relevance of the project outcomes. This request has been forwarded to ZonMw that provided the committee with additional information (see section 1.1.2).

2.2 Has the goal of the HTA methodology programme been met?

The committee agrees that the HTA methodology programme has contributed to the development and improvement of HTA methodology for application in drug efficiency research and decision-making on the efficient use and reimbursement of drugs. Part of the projects resulted in new developed methodology, other projects improved existing HTA methodology.
However, the committee wanted to have more information on the extent to which the results had impact (e.g. revision of the Dutch guidelines) in relation to the evidence from the projects funded within this programme. This question was posed to external stakeholders in the interviews and is further addressed in Chapter 3.

2.3 How is the HTA methodology programme designed and executed?

The self-evaluation reveals that stakeholders are sufficiently involved, projects were distributed equally across the major themes (Cost & Outcomes, Decision-Making, and Design & Analysis), and that quality assurance was maintained. In addition, the committee felt that it has been successful not to require a link to clinical trials as was done previously.

The committee believes that the existing process described has been highly successful. However, a first impression – based on the self-evaluation report - was that more emphasis should be given to the area of ‘decision making’, as the output in that area lags behind and supporting decision makers becomes increasingly relevant. Given the importance to provide policy relevant guidance, it was felt that policy makers, but also other stakeholders, should be involved more closely in such a programme. This was verified in the interviews with the stakeholders, which also included policy makers (see Chapter 3).

2.4 What are the results of the HTA methodology programme?

In the self-evaluation report it is stated that HTA methodology is developed and improved and that the dissemination of results to research, policy, practice and education was adequately performed and facilitated. It is concluded that the HTA methodology programme provides (even though not yet completely finished) a considerable boost in HTA research in the Netherlands. More importantly, the results can be and have been applied in drug efficiency research and decision-making on the efficient use and reimbursement of drugs but also in other fields of efficiency research and decision making.

The committee has the opinion that the self-evaluation report covers key areas of HTA methodology research. The fact that it has resulted in so many international publications shows both the high international standard and quality of HTA research in the Netherlands. Furthermore, the programme has contributed to advancing the field by maintaining and building methodological competence in the Netherlands. However, more analysis could have been done to give more insight into the contribution

to national and international policy and decision-making. This is further verified in the interviews (see Chapter 3).

2.5 Recommendations made in the self-evaluation

In the self-evaluation it is mentioned that both applied HTA research and further development of its methods is of utmost importance. The recommendations for a potential new programme are focused on two issues:

- Funding of HTA methodology projects that are not restricted to pharmaceuticals;
- HTA methodology research takes on an increasingly international perspective. Although HTA programmes may aim primarily towards the Dutch policy-making arena, collaboration and connection with international research and policy throughout Europe should as much as possible be embedded in both the design of the programme as well as in its funded projects.

The committee agrees with these viewpoints, given the increased need to support decisions that give early and sufficient access to health care while ensuring sustainability of health care systems around the globe. Funding HTA methodology projects in the area of pharmaceuticals can add value to methodological issues related to other (single) health technologies, but it would be desirable to broaden the scope towards health care in general and the optimal mix of preventive, diagnostic and therapeutic activities as this will reveal new methodological issues. To inform a potential new HTA methodology programme, it would therefore be desirable to identify gaps from both a policy and a methods perspective and opportunities for international co-operation on agenda setting and dissemination of results. This has been explored in the interviews (see Chapter 3) and via desk research (see Appendix D).

3 Views of external stakeholders

In this Chapter, the committee presents the views of ten stakeholders that were interviewed with regard to the HTA methodology programme. The stakeholders include four HTA experts/researchers, a patient representative, two policy advisors (from ZIN), two representatives from ZonMw (who are involved in a related HTA programme) and a representative from industry who is actively engaged in the Dutch society for HTA (see Appendix B). Two interviewees were also members of the appraisal committee of ZIN. Three other interviewees were also a member of the Programme Committee. Five out of the ten stakeholders have been involved in projects funded within the HTA methodology programme.

3.1 Focus of the current HTA methodology programme

All interviewees felt that the HTA-methodology programme is a unique programme. There are only a few European funding opportunities, such as Horizon 2020[2] and the Innovative Medicines Initiative (IMI)[3], but these are not particularly focused on HTA methodology. Also, in the Netherlands the possibilities for HTA methodology development outside the ZonMw methodology programme are very limited. The only example mentioned concerns the Innovational Research Incentives Scheme Veni of NWO.[4] This scheme, however, is particularly targeting researchers who have recently obtained their PhD.

Funded projects were distributed evenly across the three themes: Cost & Outcomes (19 projects), Decision Making (16 projects), and Design& Analysis (18 projects). However, the majority of the interviewees mentioned that most projects are often narrow in scope (i.e., technical) and that it would have been beneficial to show the link with policy making. It was mentioned that it is a priority to create awareness among HTA researchers to support the translation of evidence into policy and practice.

3.2 Project results and dissemination activities

The projects led to a variety of outputs, including 21 HTA tools, further research of existing methods and new theoretical insights into methodological issues regarding HTA methods and decision-making.

All interviewees underlined that the projects led to outputs, publications and increased knowledge that has supported the international profile of Dutch HTA researchers in this field. Examples include the contributions of Dutch researchers at ISPOR, IHEA and international peer reviewed journals such as Value in Health.

Also, the research theme “decision making”, which was initiated by ZIN, definitely has led to research methods and increased knowledge. In addition, a policy advisor mentioned that the HTA methodology programme has stimulated awareness regarding how to measure effectiveness, use of indirect comparisons and dealing with uncertainty.

However, the actual use of the results in policy and practice is perceived as most important to the stakeholders. Therefore, researchers should be stimulated to involve end users in their research and to make the results known to end users. This might help to successfully translate research into policy and practice.

3.3 Implementation of the results

From the interviews it became clear that HTA-researchers often perceive their research to have added value for policy and practice, but that this is not always clear to policy makers. Also, other stakeholders mentioned that there seems to be a mismatch between the development of increasingly technical, sophisticated measurement methods on the one hand, and the requirements for responsible

[2] http://ec.europa.eu/programmes/horizon2020/
[3] http://www.imi.europa.eu/content/mission
[4] http://www.nwo.nl/en/funding/our-funding-instruments/nwo/innovational-research-incentives-scheme/veni/index.html

and accountable decision making on the other hand. This might also be due to the fact that some projects were targeting a specific disease area or a specific case.

Part of the research conducted under the methodology programme definitely has led to uptake, e.g. revision of guidelines for pharmaco-economic research. For example, the updated pharmaco-economic guideline of ZIN includes a chapter that is based on the project in which a framework for real-world economic evaluations of pharmaceuticals was developed. Other projects that have been used to update the guidelines include:

- project 152002003 (Further exploration of the appropriateness of the well-being valuation method for monetary valuation of informal care) – it is recommended in the guideline to include informal care as cost category whenever relevant;
- project 152002022 (Estimating indirect medical cost and its associated uncertainty) – The guidelines specifies that indirect medical costs need to be calculated when it concerns interventions that are live-saving or which prolong life. Preferably, scenarios should be used to illustrate the results with/without indirect medical costs;
- projects 152002013/152002015 (Quality of life in expensive drugs/methods to improve piggy-back utility analysis) - In the guideline preference is given to use of EQ5D while utility mapping is not recommended;
- project 152002044 (A Dutch tariff for the EQ-5D-5L) – the guideline specifies the use of the Dutch tariff;
- projects 152002006/152002005/152002007/152002031 on VOI – As mentioned before these projects were clustered into a VIMP. The VIMP on VOI led to a chapter on the use of VOI analysis for the guideline on Outcome Research of ZIN. In addition to the guideline there are several modules, including one on VOI. This module is mainly based on the four projects funded within the HTA methodology programme.

Some interviewees mentioned that projects have not yet led to other changes in policy and practice. This may require the involvement of end users from the start of a programme (to determine what the relevant questions are) and in the preparation and execution of projects, including follow-up (after the project has been finished).

Some interviewees also refer to other countries with regard to the use of HTA in policy and practice. For example, the UK has been mentioned where NICE is collaborating more closely with academia in the UK and also with two universities from the Netherlands.

3.4 Involvement of stakeholders

Stakeholders (e.g. Ministry of Health, ZIN) were involved in the preparation and execution of the programme.

Most interviewees felt that the involvement of the stakeholders could be strengthened, both in the programme committee as well as in the execution of projects. For example, the representative of ZIN in the programme committee took an active role, which led to the research theme decision making, under which 19 projects were granted.

There have been attempts to involve policy makers (especially from ZIN) and patient representatives in projects, but this was perceived by the interviewees as limited. However, patient representatives (and health care professionals) may not always be the relevant stakeholders to be involved in methodology projects. It is therefore important to indicate if and how to involve these stakeholders in an appropriate way.

With regard to the formulation of themes for a methodology programme, several interviewees felt that it is important that policy makers should focus more on the question: what is of relevance and to whom?

Finally, one interviewee mentioned that the Dutch Society for HTA could be more actively involved, especially with regard to distributing the results of the programme.

3.5 International scope of the current programme

International collaboration is an important issue for HTA methodology development. In several projects, there has been some collaboration with other (often UK-based) research groups. However, most interviewees mentioned the need to strengthen international collaboration. Especially the use of (larger) international databases and participation in international/European research consortia should be stimulated to avoid undesirable research duplication.

An example is the collaboration with Belgium regarding reimbursement of expensive drugs (sharing of assessment reports). In addition, national researchers could collaborate more often with their colleagues abroad on important HTA methodology issues such as identified by EUnetHTA JA2 or within other European HTA methodology projects (See Appendix D).

3.6 Budget of the current programme

The majority of the projects funded under the HTA-methodology programme concern projects that focus on incremental methodological changes/adaptations. For these kinds of projects a budget of approximately 125K was seen as reasonable.

However, several interviewees mentioned that a larger budget per project is important to stimulate more innovative methodology research. In this respect, the interviewees mentioned that there should be room for both top-down (projects that lead to results in the short run (i.e., answering a concrete policy question)) and bottom-up research (innovative / in-depth theoretical/methodological projects which results could be applied in the long run). In order to subsidize both smaller and larger projects it was mentioned to use a range in stead of a fixed maximum budget per project (125K).

As mentioned above, international collaboration should be stimulated according to some interviewees. However, some other interviewees have concerns that international projects may not lead to concrete results that can be easily applied in (national) practice.

In addition, the use of VIMPs (to enhance the uptake of project results) could be used more often according to several interviewees. It is also important that VIMPs will be used to align the results from different research projects in order to increase the collaboration between the different research groups in the Netherlands.

3.7 Future programme and priorities

All interviewees had the opinion that the current HTA methodology programme is unique and should be continued to preserve and build competence in HTA methodology. A potential new HTA methodology programme should, however, not restrict its value towards one single type of technology, such as pharmaceuticals. A new programme would need to include health care in general, medical devices, procedures, prevention, organisation of care etc. In addition, the programme should be targeted towards the needs of end users in order to stimulate implementation of the results in policy and practice. Most often ZIN and the Ministry of Health were mentioned as important end users.

Some interviewees recommended a new programme with ample room for international collaboration/funding or an international programme (H2020), but other interviewees prefer a national programme.

With regard to steering of the programme, some interviewees mentioned that it is important to emphasize the multidisciplinary nature of HTA research. The multidisciplinary nature of HTA should be reflected in the programme committee and in its content. According to these interviewees the scope should be broader than cost-effectiveness only and would need to include clinical-epidemiological, legal, ethical, socio-cultural and organisational aspects as well as the policy and patient perspective. As there are several important end users mentioned, it makes sense to coordinate such a programme by an independent organisation, such as ZonMw.

With regard to themes, the following topics have been mentioned most often by the interviewees:
- Public and patient participation / stakeholder involvement / scoping /interactive technology assessment (4);

- Collecting and analysing real world data. This is already happening, but can be improved and extended. One of the most important questions is how to optimise the use of and interpret already collected data? Also, European or international collaboration is important in this respect (3);
- Big data (how to collect, analyse and use these data) (2);
- International approaches to HTAs (harmonization of methodologies across EU) (2);
- Patient preferences (2);
- Hospital-based HTA (2);
- Alternative research designs (for RCTs) (2).

4 Conclusions and recommendations

In this Chapter the external evaluation committee summarises its conclusions with regard to the self-evaluation and provides recommendations towards a potential future HTA programme. This based on desk research, on the views of ten relevant stakeholders as well as on the views and experience of the committee members.

4.1 Conclusions

The committee concludes that the HTA methodology programme has been conducted according to the assignment by the Ministry of VWS. The committee has the opinion that the self-evaluation report is very clear and comprehensive in the way the programme and its achievements are described. Overall, the self-evaluation conducted is a very well documented process review.

Taking the views from the external stakeholders and other international initiatives in the field into account, the committee believes that the HTA methodology programme is a unique programme that should be continued. There are almost no (national) funding opportunities available for HTA methodology development and it would be a missed opportunity not to preserve and increase the competence of Dutch researchers (and other stakeholders), also because there is a growing interest in this field in Europe (EU HTA network, 2014) and globally (WHO, 2014).[5]

The HTA methodology programme of ZonMw has contributed to the development and improvement of HTA methodology for application in drug efficiency research but also in other fields. Some projects resulted in new developed methodology, other projects improved existing HTA methodology. The results of several projects have been used in the revision of guidelines for pharmaco-economic research of ZIN. For example, the VIMP on VOI led to a chapter on the use of VOI analysis that is included in the updated guideline on Outcome Research.

It is, however, difficult to draw firm conclusions with regard to the actual impact of the HTA methodology programme on policy and practice at this point in time. This might be due to the fact that most of the impact is indirect (using better HTA methods that influence policy making) and that measuring the actual impact of projects too soon after the completion of the research is problematic and measuring expected impacts is difficult. It is recommended by experts in the field to wait at least six-nine years before addressing (policy) impact questions (Milat et al, 2015). It probably also would have been beneficial to engage relevant stakeholders more clearly (e.g. in selecting research themes, providing methodology training after completion of projects) as this stimulates translation of evidence in practice and policy (Lavis et al., 2008).

The fact that the programme already has resulted in many international publications and contributions to international conferences shows clearly the success of the programme. It definitely has contributed both to the high international standard and quality of HTA research(ers) in the Netherlands, as well as to advancing the HTA methodology field.

4.2 Recommendations for a future programme

The committee agrees to the recommendations made in the self-evaluation report regarding a potential new programme:

- Funding of HTA methodology projects that are not restricted to pharmaceuticals;
- HTA methodology research that takes on an increasingly international perspective.

With regard to the first point, the committee has the opinion that funding HTA methodology projects in the area of pharmaceuticals can add value to methodological issues related to other (single) health technologies, but it would be desirable to focus a new programme on health care in general and the optimal mix of preventive, diagnostic and therapeutic activities as this will reveal new methodological issues compared to the focus on one single health technology.

[5] http://ec.europa.eu/health/technology_assessment/docs/2014_strategy_eucooperation_hta_en.pdf

Before starting a new (HTA methodology programme the committee recommends to contact organizations that have invested in studies to identify policy issues that can be (partly) solved by improving HTA methods and have set priorities for HTA methodology research. Examples of such organisations include NICE in the UK, TLV[6] and SBU in Sweden and PCORI[7] in the US (see also Appendix D). The priority lists of these organizations may inform top-down research of such a new programme, but emphasis should be given to priorities based on an inventory of relevant policy issues in Dutch health care. Regarding the latter, the committee has the opinion that more research should be conducted to help construct a policy decision framework for reimbursement decisions (cost-effectiveness threshold, position of criteria such as disease burden and patient characteristics, broader definition of effectiveness, etc.). Another important policy issue (in the Netherlands) concerns the use of cost-effectiveness information in price negotiations with pharmaceutical companies and other health care suppliers.

It is recommended to organise a workshop with relevant Dutch policy makers to identify the most relevant issues more in-depth. Consideration of foreign priority lists for methodological research may also reveal opportunities for pooling research funds and increased international collaboration between HTA-researchers. Furthermore, the committee recommends building on the experiences of researchers in the current HTA methodology programme. A workshop with selected coordinators of the most successful projects may help to identify important methodological gaps that are linked to Dutch policy issues. Both workshops may inform the formulation of top-down research priorities. However, the committee also believes that there should be room for bottom-up research in a new HTA methodology programme, as this has been a successful strategy in the current programme.

In addition, the committee would like to make the following suggestion regarding the process of the programme:

- Strengthen the involvement of stakeholders (policy makers, patients, health professionals), both in the programme committee as well as in the execution and follow-up of projects where relevant;
- Focus a new HTA methodology programme on questions that are relevant from the perspective of the end user(s) in the Netherlands (i.e., ZIN, Ministry of Health) but also from a societal perspective. Some policy makers will focus on their respective budgets but it important to also focus on efficiency from a societal perspective, including broader societal benefits;
- Be aware of and collaborate with (international) initiatives to address relevant research priorities in order to avoid duplication and to stimulate potential international collaboration on important HTA methodology issues (see Appendix D);
- Stimulate both top-down as well as bottom-up research;
- Disseminate the results of the programme more actively to end users and other relevant stakeholders, e.g. by stimulating the researchers to present their results at national symposia, provide a booklet with summaries of the project results and involve the Dutch society for HTA in dissemination activities;
- Make more use of VIMPs to enhance the uptake of project results in decision making, e.g. by providing training to end users in order to understand and use the methods. In this respect the committee recommends to consider the experience with VIMPs in the current HTA methodology programme to identify which activities have been most successful.

Regarding topics for a new HTA methodology programme, the committee refers to the activities above as this will inform ZonMw about potential priorities. However, the committee believes that building a decision making framework for reimbursement decisions is very important, including issues around the value of a QALY, measuring real opportunity costs, end of life treatment etc. Also, the committee acknowledges that treatment strategies are becoming much more complex, including careful sequencing of preventive, diagnostic and therapeutic activities over different disease cycles, often targeted towards elderly with multiple morbidity. This requires new practices to address these complex optimization problems.

[6] http://www.tlv.se/In-English/in-english/
[7] http://www.pcori.org/about-us

List of references

Andrew J. Milat, Adrian E. Bauman, Sally Redman (2015). A narrative review of research impact assessment models and methods. Health Research Policy and Systems 13: 18.

EU Health Technology Assessment Network (2014). Strategy for EU Cooperation on Health Technology Assessment. Available at: http://ec.europa.eu/health/technology_assessment/docs/2014_strategy_eucooperation_hta_en.pdf

EUnetHTA (2015). Letter to Dr. Ruxandra Draghia-Aklia, Director Directorate E - Health. DG Research and Innovation. Available at: http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/EUnetHTALetter%20to%20DG%20RI%20on%20HTA%20in%20Horizon2020_final_20150312.pdf

HAS (2015). Forum HAS Health Technology Assessment sans frontières - Paris - 30 Octobre 2015. Available at: http://www.has-sante.fr/portail/upload/docs/application/pdf/2015-07/collhas_2015_programme_detaille_2015-07-22_11-07-33_440.pdf

Joore, M.A. (2013). Revision pharmaco-economic guidelines and manual cost research, Maastricht UMC+.

J.N. Lavis, A.D. Oxman, R. Moynihan, E.J. Paulsen (2008). Evidence-informed health policy 1 - Synthesis of findings from a multi-method study of organizations that support the use of research evidence. Implementation Science 3: 53. Available at http://www.implementationscience.com/series/Evidence_informed_health_policy

Maiwenn Al, Jill Bindels, Isaac Corro Ramos, Talitha Feenstra, Janneke Grutters, Manuela Joore, Saskia Knies, Hao Le, Leyla Mohseninejad, Maarten Postma, Bram Ramaekers (2014). Value of information and its use in decision making concerning (conditional) reimbursement of health technologies in The Netherlands, ZonMw.

Van den Akker-van Marle, M.E. and A. Van Sonsbeek (2015). Evaluation Health Technology Assessment Methodology Programme, ZonMw

World Health Organization (2014). Health intervention and technology assessment in support of universal health coverage. Sixty-seventh World Health Assembly. WHA67.23 Agenda item 15.7. Available at: http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R23-en.pdf?ua=1

A External Evaluation Committee

– Professor dr. Frans Rutten (chair)
Frans Rutten is emeritus professor of Health Economics at the Erasmus University Rotterdam and was head of the department of Health Policy and Management from 2002 until 2007. From 1988-2000 he was managing director of the institute for Medical Technology Assessment, which he founded. He has served in various advisory bodies to the Dutch government, the European Commission, the WHO, the Council of Europe and the pharmaceutical industry. In addition, he has acquired numerous research grants from the European Commission, WHO, international and national research funds and pharmaceutical companies. He served as president of the international Health Economics Association (iHEA) in 2001-2002.

– Professor dr. Allan Wailoo (UK)
Allan Wailoo is professor of Health Economics at the University of Sheffield (School of Health and Related Research (ScHARR)/Health Economics and Decision Science). He joined ScHARR in 2000 having previously worked at the University of Leicester where he was awarded a Personal Chair in 2012.

He is also Director of the NICE Decision Support Unit and a member of the Research Design Service for Yorkshire and the Humber. In addition, he is a member of the NICE Medical Technologies Appraisal Committee (MTAC) and Sub Panel Member of the NIHR Programme Grants for Applied Research.

– Professor dr. Bengt Jönsson (Sweden)
Bengt Jönsson is emeritus professor of Health Economics at the Stockholm School of Economics (SSE), Sweden. Before joining the SSE in 1990 he was a professor at Linköping University, Department of Health and Society, 1982-1990. He was director of the Swedish Institute for Health Economics (IHE) in Lund from 1979 to 1982, and a member of the IHE Board until 2004. He is now chair of IHE scientific advisory board. He is also a member of the European Academy of Cancer Sciences, and vice chair of the EU Expert Panel on effective ways of investing in health.

Professor Jönsson is a member of the editorial boards of several journals, including the European Journal of Health Economics, and International Journal of Technology Assessment in Health Care. He has also been a temporary adviser to the WHO and a consultant to OECD and UNIDO. Professor Jönsson's extensive publications in the field of health economics include over 200 papers, reports, and book chapters. Presently he is president of the SHEA, the Swedish Health Economics Association and past president of iHEA, the international Health Economists Association.

– Dr. Wija Oortwijn (secretary)
Wija Oortwijn is manager of the health unit at Ecorys Netherlands B.V. She has more than 20 years of relevant professional experience in HTA and health policy analysis. She led for example a project on the impact of HTA on prescribing patterns of diabetes and rheumatic arthritis drugs in Europe, the US, Canada and Australia. More recently, she developed an instrument to map the level of HTA at country level. This was applied to selected middle-income countries (Argentina, Brazil, India, Indonesia, Malaysia, Mexico and Russia) as well as to countries well-known for their comprehensive HTA programs (Australia, Canada and United Kingdom).

She has coordinated and participated in different European collaboration networks focusing on HTA (Eurassess, HTA Europe, ECHAHI/ECHTA that resulted in EUnetHTA. She is a founding Member of the Dutch and International Society for HTA (NVTAG and HTAi) and is involved in the organisation annual HTAi conferences. Furthermore, she is a member of the Editorial Board of the International Journal of Technology Assessment in Health Care.

B Interviewees

HTA-researchers	
Prof. Dr. GJ van der Wilt	Professor of HTA at Radboudumc, Nijmegen / member of the Appraisal Committee (National Health Care Institute - Zorginstituut Nederland (ZIN))
Prof. Dr. H. Severens	Professor of Evaluation in Health Care at the Institute of Health Policy and Management and the Institute of Medical Technology Assessment at Erasmus University Rotterdam / vice chairman of the Health Council / Member of the HTA methodology programme committee (short period)
Prof. Dr. M.J. Postma	Professor in Pharmaco-economics at the University of Groningen, Department of Pharmacy, Unit of PharmacoEpidemiology & PharmacoEconomics
Dr. M.A. Joore	Associate professor at the Maastricht University Medical Centre (Dept. Clinical Epidemiology and Medical Technology Assessment) / Member of the HTA methodology programme committee
Policy makers	
Dr. W.G. Goettsch	Policy advisor at the National Health Care Institute and WP-leader within the EUnetHTA JA2 / Member of the HTA methodology programme committee
Dr. S. Knies	Policy advisor at the National Health Care Institute – working on the revision of pharmaco-economic guidelines
Industry	
Dr. M. van Agthoven	Associate Director Market Access at Gilead / Board member of the Dutch Society for Health Technology Assessment
Patients	
Dr. C. Smit	Patient advocate / member of the Appraisal Committee (National Health Care Institute - Zorginstituut Nederland (ZIN))
ZonMw	
Dr. M. Sneijders Dr. K. van Liere-Visser	Mariëlle Sneijders is coordinator of the Health Care Efficiency Programme (DO programme) at ZonMw. Karen van Liere-Visser is programme secretary of the DO programme.

C Interview guide

Introduction

1. Could you please specify your position and your involvement with respect to the topic/programme under study?

Focus/priorities

Funded projects were distributed evenly across the three themes: Cost & Outcomes (19 projects), Decision Making (16 projects), and Design& Analysis (18 projects).

2. Looking back, have there been any (international) research gaps that were not addressed within this HTA methodology programme but should get priority in a next programme?
3. What are current and future priorities for HTA methodology - both from a policy and research methods perspective?
4. Are there any other funding opportunities for such HTA methodology research besides the ZonMw programme?
5. Which of these priorities should certainly be addressed in a (new) HTA methodology research programme?

Stakeholder involvement

Stakeholders (e.g. Ministry of Health, National Health Care Institute – ZIN) were involved in the preparation and execution of the programme. Furthermore, they were often asked to be consultants or advisors within project teams.

6. What are the main advantages and disadvantages of stakeholder involvement in this programme?
    a. Has the involvement of stakeholders really resulted in methods outputs that are geared to the requirements of Dutch decision making bodies?
    b. How could it be improved?
7. Would changes regarding stakeholder involvement be beneficial for a potential future HTA programme? If so, how?

Budget

The total budget of the HTA methodology programme was 6.4 million Euros; the maximum budget per project was 125K Euros.

8. Was the funding sufficient for each individual project taking into account the aim of the programme?
9. Is there any case for more expensive, longer duration projects, at the expense of the number of projects funded under the (next) programme (53)?

Process

10. To what extent has the steering process of the programme been successful in obtaining its main aim? Would changes here be beneficial?
11. To what extent should there have been cooperation with other, national or international, funders to make more efficient use of funds, to ensure there is no undesirable duplication, and to consider jointly funding projects, that may also involve research groups from different countries?
12. To what extent can/have internationally based researchers bid for research funds from this methodology programme either as PIs or in collaboration with Dutch universities? Would changes here be beneficial?

13. There are a high number (27) of reports that require additional work for approval at the end of the project. Should there be a requirement for each project to have something similar to a trial "steering committee" to better ensure progress and delivery to budget and timetable?

Results

The projects led to a variety of outputs, including 21 HTA tools, further research of existing methods and new theoretical insights into methodological issues regarding HTA methods and decision-making.

14. To what extent has the programme contributed to national and international methods development and improved (drug) decision-making?
15. Which factors seem to be associated with the successful translation of research in changing methodological guidance, policy and practice?
16. Is the dissemination of the programme results successful a) within the Netherlands and b) internationally?
17. What is the contribution of the programme results towards a) the international methodological knowledge base and b) the profile of Dutch HTA researchers in this field?

Looking forward

18. Would you recommend a new HTA methodology programme? If so:
    - Should this programme be a national, European and/or international research programme?
    - Should this programme be targeted towards one single area such as pharmaceuticals, medical devices etc.?
    - Which lessons can be learned from other European/international experiences?
    - What other important issues should be taken into account?

Thank you for your cooperation!

D Selection of HTA methodology initiatives

In order to inform a potential new HTA methodology programme, the committee believes that it is important to be aware of relevant initiatives in the field of HTA methodology. These include amongst others, the EUnetHTA JA, FP7 projects as well as the MRC/NIHR Methodology Research Programme in the UK and the work undertaken by the Swedish Council on Technology Assessment in Health Care (SBU).

EUnetHTA

Since 1993, the European Commission (EC) supported important projects on HTA that resulted in a European collaborative network (EUnetHTA).[8] EUnetHTA was established to create an effective and sustainable network for HTA across Europe. Since 2009, the EUnetHTA is co-funded by the EU (Health Programme) in a Joint Action. The objectives of EUnetHTA JA2 (2012-2015) are:

- To strengthen the practical application of tools and approaches to cross-border HTA collaboration
- To bring collaboration to a higher level resulting in better understanding for the Commission and Member States of the ways to establish a sustainable structure for HTA in the EU
- To develop a general strategy, principles and an implementation proposal for a sustainable European HTA collaboration according to the requirements of Article 15 of the Directive for cross-border healthcare.

EUnetHTA also performs the function of the scientific and technical cooperation of the HTA Network.[9] The EC will probably propose a new Joint Action on HTA in its Health Programme, to which EUnetHTA will apply to continue its activities for the coming three years.

Earlier this year, EUnetHTA has sent a letter to DG Research and Innovation to inform them about the latest scientific developments in the field of HTA (EUnetHTA, 2015) as input for the Horizon 2020 programme. The methodological issues that require further research according to EUnetHTA include:

- Alignment of HTA use at different levels: HTA can be used for hospitals' decision-making on the availability and pricing of new technologies, to the regional and national level where HTA information is used for decisions on reimbursement of health technologies;
- The importance of additional patient data collection for HTA;
- Synergy between HTA and clinical guideline development as incentives for appropriate use of healthcare;
- Research into organisation of care and systems research;
- Specific attention to advanced innovative medical devices and other advanced technologies;
- Transferability of cost-effectiveness data;
- Research methodologies to better capture patient perceptions and preferences.

FP7 projects

The EC has funded within the FP7 HEALTH programme (2012-2015) four HTA research projects that include methods development. The projects are:

- INTEGRATE-HTA - Adaptation and development of concepts and methods for HTA to enable an integrated assessment of issues of complex technologies (www.integrate-hta.eu);
- AdoptHTA - Adopting Hospital Based Health Technology Assessment in EU (http://www.adhophta.eu/);
- AdvanceHTA - Advancing and strengthening the methodological tools and practices relating to the application and implementation of Health Technology Assessment (http://www.advance-hta.eu/);
- MedtecHTA - Methods for Health Technology Assessment of Medical Devices: a European Perspective (http://www.medtechta.eu/wps/wcm/connect/Site/MedtecHTA/Home/);

The first two projects aim to develop concepts and methods that enable a patient-centred, comprehensive assessment of health technologies. HTA has traditionally focused on effectiveness and economic aspects of technologies and has paid less attention to ensuring that HTA reports are translated into a message that is meaningful to users and decision-makers at micro-, meso- and macro-level. The latter two projects focuses on ways forward to overcome some of the methodological

[8] http://www.eunethta.eu

[9] This is a voluntary network set up by Article 15 of Directive 2011/24. See for more information: http://ec.europa.eu/health/technology_assessment/docs/2014_strategy_eucooperation_hta_en.pdf.

challenges in current practices of HTA for medicines and medical devices. Currently, value assessment have been subject to criticism about whether these measures capture all the important dimensions of value, including living with the disease and receiving treatment in real world settings, while adequately recognising and valuing innovation. Difficulties also arise in terms of assessing the value of particular technologies in the absence of comparative efficacy data, as is often the case with medical devices (HAS, 2015).

Methodology Research Programme in the UK

The Medical Research Council (MRC) and the National Institute for Health Research (NIHR) in the UK fund methodology research through the MRC/NIHR Research Programme.[10] The programme is governed by the MRC, using independent experts and the MRC Methodology Research Panel[11] to review applications that can be submitted twice a year.

The MRC/NIHR Methodology Research Programme funds methodology research including:

- Methods development to underpin the biomedical and health-related sciences, with methodological outputs that are applicable beyond a specific case study;
- 'Methods in research' for developing methods and their implementation in research standards with the aim of improving quality and consistency in practice, for example consensus statements.

The current priorities are:

- Observational data in clinical decision making;
- Multiple testing/subgroup analyses;
- Missing data and propensity scores;
- Assessing quality of life in carers;
- Improved measurement methods for population science research;
- Methodology for stratified medicine;
- Improving cross-sector comparisons; Beyond QALY;
- Methodology for Eliciting Expert Opinion.

Grants can be awarded up to five years; projects with a duration of two years or less are classified as proof of principle or pilot work.

Swedish Council on Technology Assessment in Health Care (SBU)

SBU, one of the first HTA agencies around the globe, was established in 1987 in the Government Office of Sweden. In 1992, SBU became an independent, public body with the same mandate.

It aims to provide unbiased scientific HTA to identify effective and ineffective health practices in different patient groups to improve health services and to critically review the scientific basis of methods used in health care. From mid-2015 onwards, the government has commissioned SBU to also evaluate the scientific evidence of methods regarding social services.

SBU has been and is active in the global development of HTA. It was part of the first HTA collaborative initiatives in Europe (Eurassess, HTA Europe, ECHAHI/ECHTA) that resulted in the EUnetHTA network. As part of the strategy for 2016-2018, SBU will give priority to international HTA methodology development, e.g. GRADE-system, handbook of HTA and modelling of health economic analysis.[12]

[10] http://www.mrc.ac.uk/funding/browse/methodology-research-programme/
[11] http://www.mrc.ac.uk/about/research-boards-panels/methodology-research-programme-panel/
[12] http://www.inahta.org/our-members/members/sbu/

Health Technology Assessment Methodology Programme

Evaluation

April 2015

Colophon

ZonMw is The Netherlands Organisation for Health Research and Development

Progress requires research and development. ZonMw funds health research and stimulates use of the knowledge developed to help improve health and healthcare.

ZonMw's main commissioning organisations are the Ministry of Health, Welfare and Sport and the Netherlands Organisation for Scientific Research.

For further information on this publication or the programme, please contact Benien Vingerhoed through e-mail Farmacotherapie@zonmw.nl or by telephone +31 (0)70 349 53 29 of +31 (0)70 349 53 00.

Authors: M.E. van den Akker-van Marle, A. van Sonsbeek
Date: April 2015

ZonMw
Laan van Nieuw Oost-Indië 334
2593 CE The Hague
P.O. Box 93245
2509 AE The Hague
The Netherlands
Phone +31 (0)70 349 51 11
Fax +31 (0)70 349 51 00
info@zonmw.nl
www.zonmw.eu

RECOMMENDATIONS FOR THE FUTURE

Health technology assessment (HTA) is a multi-disciplinary field of policy analysis that studies the medical, social, ethical, and economic implications of development, diffusion, and use of health technology[1]. Rising health care costs and new technical possibilities put higher demands on the substantiation and transparency of decision-making to ensure a sustainable health care system. This is also increasingly recognized in society, as reflected by the fact that cost-effectiveness is part of the Coalition Agreement of the Dutch government parties People's Party for Freedom and Democracy (VVD) and Labour Party (PvdA) of October 29, 2012[2]. Furthermore, in a survey among 2000 Dutch medical specialists in the summer of 2014, as many as 71 percent of the surveyed experts indicated to be in favor of a ceiling on prices in care[3]. Also, consecutive agreements are concluded by the government, health care providers, health insurers and patient organizations to achieve an affordable and sustainable health care system[4,5] and several scientific associations of medical specialists have drawn up a priority list of care evaluations for which the greatest improvement is anticipated when it comes to both quality of care and cost savings[6]. These developments ask for both applied HTA research and further development of its methods. HTA research, applied and methodological, is therefore of utmost importance.

The importance of methodological HTA research is acknowledged by the Ministry of Health, Welfare and Sport (VWS) while approving the execution of an HTA methodology programme as part of the Expensive and Orphan Drugs Programme (EODP). The preeminent goal of the HTA methodology programme was to develop and improve HTA methodology for application in drug efficiency research and decision-making on the efficient use and reimbursement of drugs.

At present, the HTA methodology programme, although not yet completely finished, has already made a considerable boost in HTA research in The Netherlands. A total of 53 projects have been approved which has resulted in the development of 21 HTA tools so far, further investigation of existing methods and new theoretical insights into methodological issues regarding HTA research and decision making. Dissemination was performed by publications (69 until now), presentations, workshops and symposia. The fact that proposals did not have to be related to a clinical trial as was necessary in a previous programme, resulted in a broad-spectrum of HTA research being carried out.

The programme has directly improved national guidelines for health care research, which contributed to transparent and evidence-based decision-making on the efficient use and reimbursement of drugs and other health care. It has also contributed to a good international reputation of Dutch HTA methodology.

Future programmes on HTA research are necessary to build on the current results and to address new methodological research questions. In this way the international reputation of Dutch HTA methodology research can be maintained. In addition, while the current HTA methodology programme is linked with the EODP, future programme design should consider the funding of HTA tools that are not restricted to pharmaceuticals. For instance, new and validated HTA tools are needed in the field of disease prevention and diagnostics and the areas of youth care, care for older persons, nursing and medical devices. From a societal perspective such HTA tools can have a large impact on decision-making for healthcare.

Furthermore, it is important to note that HTA methodology research takes on an increasingly international perspective. Although HTA programmes may aim primarily towards the Dutch policy-making arena, collaboration and connection with international research and policy throughout Europe should be embedded in both the design of the programme as well as its funded projects.

[1] http://www.inahta.org/hta-tools-resources/
[2] http://www.rijksoverheid.nl/documenten-en-publicaties/rapporten/2012/10/29/regeerakkoord.html
[3] http://www.demedischspecialist.nl/nieuws/meerderheid-medisch-specialisten-vindt-prijsplafond-voor-behandelingen-onvermijdelijk
[4] http://www.rijksoverheid.nl/documenten-en-publicaties/besluiten/2011/07/05/bestuurlijk-hoofdlijnenakkoord-2012-2015.html
[5] http://www.rijksoverheid.nl/documenten-en-publicaties/kamerstukken/2013/04/24/kamerbrief-over-resultaten-zorgoverleg.html?utm_source=twitterfeed&utm_medium=twitter
[6] SEENEZ = Stimulate Effective and Eliminate non-Effective Care

SUMMARY

In August 2007, the Ministry of Health, Welfare and Sport (VWS) approved the execution of the Expensive and Orphan Drugs Programme (EODP) with an allotted budget of € 24.05 million. Of this budget, €6.4 million was designated for the Health Technology Assessment (HTA) methodology programme. The preeminent goal of the HTA methodology programme was to develop and improve HTA methodology for application in drug efficiency research and decision-making on the efficient use and reimbursement of drugs. The following themes were defined by the programme committee: *Costs & Outcomes, Decision-making* and *Design & Analysis*. Only applications that focused on one of these predetermined themes were accepted.

There were six calls for proposals in the years 2008 to 2011. A total number of 193 project ideas was submitted throughout these calls, 105 were expanded to full proposals, resulting in 53 projects granted funding. Projects were distributed equally across the research themes. Projects were not evenly distributed across the various research institutes in The Netherlands.

The start and progress of almost all projects went well. Some projects had delays beyond the 6-month start-up period. For the majority of the projects the mid-term progress report was directly approved. At present, 38 end-term reports have been approved, 14 projects are still ongoing and one project was stopped prematurely due to issues with research staff. Of the finished projects, 28 projects (75%) fully delivered the results they aimed to produce. The other projects partially delivered the promised results due to various circumstances; however, the knowledge produced in these projects is regarded as valuable.

Stakeholders were involved in the preparation and execution of the programme. Representatives from the Ministry of VWS and the National Health Care Institute (ZIN), both policymaking institutions, were directly involved in the development of the programme text. Both organisations also had non-voting members within the programme committee, who took part in discussions regarding programme strategy and funding of projects. Furthermore, they were often asked to be consultants or advisors within project teams. However, future programmes should ideally involve these stakeholders from the start as project team members, dedicating time to the project itself and contributing to project quality and implementation. HTA experts were directly consulted in the development of the programme and call texts, and featured in the programme committee for the selection of projects. Also, HTA project leader meetings were organised to inform HTA professionals about the ongoing projects and their results.

A total of 21 HTA instruments for use in practice is developed so far, consisting of questionnaires, models and practical tools. Next to the development of new instruments, existing methods are investigated further and new theoretical insights into methodological issues regarding HTA research and decision making have been obtained. The results of the majority of the finalised projects filled knowledge gaps in HTA methodology that can be used in the revision of ZIN guidelines for health outcome research, i.e. the pharmaco-economic guideline, the guidance for outcome research and the cost manual. To date, 69 articles have been published in peer-reviewed journals as a result of funded research (and 47 articles are in the preparation phase). Further dissemination of results was performed by presentations, workshops and symposia. Results of the projects can be used in policy, research, education and clinical practice.

The current evaluation reveals that stakeholders are sufficiently involved, projects were distributed equally across the major themes, quality assurance was maintained, HTA methodology was developed and improved and dissemination to different sectors (research, policy, practice and education) was adequately performed and facilitated.

All together, the HTA methodology programme, although not yet completely finished, has already made a considerable boost in HTA research in The Netherlands which can be applied in drug efficiency research and decision-making on the effective and efficient use and reimbursement of drugs but also in other fields of HTA research and decision making. The fact that proposals did not have to be related to a clinical trial as was necessary in a previous programme, resulted in a broad-spectrum of HTA research being carried out. This resulted also in a good international reputation of Dutch HTA methodology research as evidenced by prominent presence of Dutch researchers at HTA congresses (e.g. ISPOR), successful acquisition in international funding (e.g. Horizon 2020) and the involvement

of Dutch researchers in the technology appraisals of the National Institute for Health and Care Excellence (NICE) in the United Kingdom

The majority of the projects did result in a need for further research, as both the existing research questions ask for more research and new research questions have arisen, indicating the need for continuation of the HTA methodology programme. Moreover, as in the current HTA methodology programme the link with the EODP was mandatory, the programme committee noticed that projects were regularly narrowed in this respect, while a wider focus would have been interesting. Also, many opportunities for HTA research beyond pharmaceutical drugs, could not be addressed.

Index

Appendices

LIST OF ABBREVIATIONS

ACP	Insured Package Advisory Committee
CIP	Communication and Implementation Plan
ECHE	European Conference on Health Economics
EODP	Expensive and Orphan Drugs Programme
Erasmus MC	Erasmus Medical Centre
EUR	Erasmus University Rotterdam
HTA	Health Technology Assessment
iHEA	international Health Economics Association
iMTA	institute for Medical Technology Assessment
ISPOR	International Society For Pharmacoeconomics and Outcomes Research
LolaHESG	The Low Lands Health Economists' Study Group
LUMC	Leiden University Medical Centre
MCDA	Multi Criteria Decision Analysis
MUMC	Maastricht University Medical Centre
NICE	National Institute for Health and Care Excellence
NVTAG	Dutch Society for Health Technology Assessment
NWO	The Netherlands Organisation for Scientific Research
NZA	Dutch Healthcare Authority
PvdA	Labour Party
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RIVM	The National Institute for Public Health and the Environment
SMDM	Society for Medical Decision Making
UMCG	University Medical Centre Groningen
UMCN	University Medical Centre Nijmegen
UMCU	University Medical Centre Utrecht
VGE	Dutch-Flemish Health Economics Association
VIMP	Dissemination and Implementation Impulses
VOI	Value of Information
VU	VU University Amsterdam
VVD	People's Party for Freedom and Democracy
VWS	Ministry of Health, Welfare and Sport
ZIN	The National Health Care Institute
ZonMw	Dutch Organisation for Health Research and Development

1. Introduction

This report details the evaluation of the Health Technology Assessment (HTA) Methodology Programme, from the start of the programme (August 2007) up to and including December 2014. However, as some projects are even ongoing, its full impact cannot yet be established.

1.1 Evaluation goal

The goal of the evaluation is the justification of the programme budget to the sponsor of the programme, the Ministry of Health, Welfare and Sport (VWS). The report will therefore give insight into the execution and the results of the programme.

1.2 Methods

The evaluation of the HTA methodology programme consists of an (internal) self-evaluation and an evaluation by an independent external committee. This report describes the self-evaluation conducted by ZonMw and the Programme Committee. The external committee will be asked to objectively assess and validate the conclusions and recommendations of the self-evaluation.

The self-evaluation is drafted on the basis of the following questions, `terms of reference':

1. Has the goal of the HTA methodology programme been met?
2. How is the HTA methodology programme designed and executed?
   a. Have the stakeholders of the programme sufficiently been involved in the preparation and execution of the programme?
   b. How is the quality of the programme and its funded projects assured?
   c. How are the projects distributed per theme?
3. What are the results of the HTA methodology programme?
   a. Which products are delivered by the projects?
   b. In which ways are new knowledge and/or instruments being disseminated?
   c. In which sector are results being used (research, policy, practice, education, etc.)?

The information for the self-evaluations is obtained from

- Programme calls
- Mid term and end term reports of projects
- Update of project output as delivered by the project leaders
- Communication and implementation plan for the HTA Methodology Programme (IMTA 2010)
- Report 'Revision pharmaco-economic guidelines and manual cost research' (MUMC 2013)[7] and updates in April 2015.

1.3 Report layout

In Chapter 1 the goal of the evaluation, the method and layout of this report are presented. In Chapter 2 the questions of this evaluation are answered. In Chapter 3 and 4 more background information is given about the design and execution of the HTA methodology programme and the results of the HTA methodology programme. The recommendations for the future and the summary are listed at the beginning of the report.

[7] http://www.zonmw.nl/nl/publicaties/detail/revision-pharmaco-economic-guidelines-and-manual-cost-research/?no_cache=1&cHash=eed1cc034a056c941c2d6ae353a3996b

2. Evaluation

In this chapter the results and conclusions of the 'terms of references' formulated in Chapter 1 are described.

2.1 Has the goal of the HTA methodology programme been met?

The HTA programme has contributed to the development and improvement of HTA methodology for application in drug efficiency research and decision-making on the efficient use and reimbursement of drugs. Part of the projects resulted in new developed methodology, other projects improved existing HTA methodology. The fact that proposals did not have to be related to a clinical trial as was necessary in a previous programme, resulted in a broad-spectrum of HTA research being carried out. However, the majority of the projects resulted in a need for further research, as both the existing research questions ask for more research and new research questions have arisen, indicating the need for further development and improvement of HTA methodology, also beyond the link with pharmaceutical drugs.

2.2 How is the HTA methodology programme designed and executed?

2.2.1 Have the stakeholders of the programme sufficiently been involved?

Primary stakeholders were involved in the preparation and execution of the programme. We define primary stakeholders to include those most likely to benefit directly from programme results; in particular, HTA researchers from research institutions and pharmaceutical industries who directly employ the results of their research, and policymakers who can use HTA tools to inform reimbursement decisions and guidelines. Secondary, indirect stakeholders include certain pharmaceutical industries and patients, as the research and reimbursement decisions made by the primary stakeholders affect the availability of drugs of treatment and manufacturing. The involvement of the primary stakeholder groups in the design and execution of the HTA methodology programme will be discussed in the following sections.

Policy Makers

Representatives from the Ministry of VWS and the National Health Care Institute (ZIN), both policymaking institutions, were directly involved in the development of the programme text. In the programme text the identified knowledge gaps in the ZIN 'Guidance for Outcomes Research for the assessment of the cost-effectiveness of in-patient medicines' report were addressed. Both organisations have non-voting members within the programme committee, who take part in discussions regarding programme strategy and the funding of projects. In this manner, the interests of policymakers are taken into account. Moreover, since 2006, several annual meetings have been held involving stakeholder representatives from ZonMw, Ministry of VWS, ZIN, and Dutch Healthcare Authority (NZA) to discuss the overarching EODP programme strategy. Within these meetings, the execution of the HTA methodology programme and its research themes and priorities are discussed, with outcomes driving the adaption of programme strategy.
Representatives from organisations such as ZIN were often asked to be consultants or advisors within the project team; however, future programmes should ideally involve stakeholders from the start as project team members, dedicating time to the project itself and contributing to project quality and implementation.

HTA Professionals

The initiation of the HTA methodology programme was supported by researchers, who expressed enthusiasm for increased funding of research for the development of HTA tools for decision-making. ZonMw responded through the establishment of this programme; previously proposals could only be submitted if linked to a clinical trial, but under the HTA methodology programme, also proposals apart from clinical trials were eligible for funding.
HTA experts were directly consulted for the development of the programme and call texts, as well as in priority-setting for research themes. HTA experts were not only featured in the programme committee for the selection of projects, they also drafted the Communication and Implementation Plan (CIP) on commission by ZonMw. Also, HTA Project Leader meetings were organised, partly together with the NVTAG. In this way HTA professionals were informed about the ongoing projects and their results, and further interaction between HTA professionals was enhanced.

This programme also provided funding in support of the scientific careers of PhD researchers and post-docs. The overall contribution to the field of HTA through this programme has allowed them to advance the position of Dutch HTA research worldwide.

2.2.2 How is the quality of the programme and its funded projects assured?

Quality assurance was maintained from start to finish, on both the programme level and project level. The content of the programme was continuously monitored and adjusted to meet the needs of involved stakeholders, as well as to respond to new developments in the field of HTA. The collaboration amongst the Ministry of VWS, ZIN, and HTA researchers ensured an expansive design for a quality programme responsive to many areas of research and action. Project selection was also done by a multi-disciplinary committee including HTA experts, physicians, epidemiologists, pharmacologists, pharmacists and patient representatives. This combination of expertise made it possible to identify projects with the potential to lead to new HTA tools for broad societal impact. Selection procedures ensured that funded projects, while having strong scientific bases, were not a purely scientific exercise; projects were also selected based on potential impact in society. At the project level, project leaders were required to submit mid-term reports, which are reviewed to reflect on current (or overall) progress, necessary adjustments, and provide the approval necessary for the project and funding to continue. These reports are supplemented by later end-term reports completed by project leaders following the conclusion of research. These measures contributed to ensuring the quality of funded projects.

2.2.3 How are the projects distributed per theme?

Projects were distributed equally across the major themes of Cost & Outcomes, Decision-Making, and Design & Analysis. This helped to ensure that all themes received adequate research attention. Considerable attention and priority were given to the funding of projects that focus on gaps within these three major themes. In the area of Costs & Outcomes, tools were developed in previously unaddressed areas such as measuring the quality of life in patients with dementia (this project won the Quality Prize in 2012). In the area of Design & Analysis, knowledge gaps pertained to policy development for the conditional reimbursement of expensive and orphan drugs; for example, a project addressed how to utilize n=1 studies in reimbursement decisions. For the theme Decision-Making, projects addressed gaps such as models for the determination of the value of quality adjusted life years (QALY) gains to aid in the Dutch decision-making model and a checklist to assess whether the HTA is generalizable to the decision context is developed. The aforementioned projects are examples of ways in which the funded research responded to knowledge gaps within the field of HTA methodology, and particularly within the three highlighted themes.

2.3 What are the results of the HTA methodology programme?

2.3.1 Which products are delivered by the projects?

Project output was broad and included new knowledge and instruments for use in practical decision-making by policymakers and HTA professionals. So far, 21 instruments have been developed, which address a wide variety of research gaps in the field of HTA (see Appendix 2). The resulting knowledge and instruments are useful across various fields such as policy, research, education, and clinical practice, e.g. the results of the majority of the finalised projects can be used in the revision of ZIN guidelines[8]. As several projects are not yet finalised, it is likely that further knowledge and instruments will be produced.

2.3.2 In which ways are new knowledge and/or instruments being disseminated?

Dissemination and implementation activities were guided by the CIP, which outlines communication and implementation activities on the project and programme level. To date, as a result of funded research 69 articles have been published in peer-reviewed journals (47 are in the preparation phase, and all funded projects can be accessed via the ZonMw website). Dissemination of results was successfully organised not only through journal publications, but also through presentations, workshops, and symposia. Research within the programme has resulted in 77 presentations aimed at HTA professionals. Theme discussions amongst project leaders were organised to initiate the synthesis of new knowledge generated by their research. Furthermore, collaboration with the

[8] http://www.zonmw.nl/nl/publicaties/detail/revision-pharmaco-economic-guidelines-and-manual-cost-research/?no_cache=1&cHash=eed1cc034a056c941c2d6ae353a3996b

Maastricht University Medical Centre (MUMC) led to the identification of project results for inclusion in revised ZIN guidelines, representing a key step towards implementation.
Furthermore, several VIMPs are and will be funded for supplementary implementation activities. Projects for which dissemination and implementation are needed, receive support to improve in this area.
Finally, ZonMw will prepare a publication on the results of the HTA methodology programme aimed at the general public.

2.3.3 In which sector are results being used?

The results of the projects can be used in policy, research, education and clinical practice. Policy and research are the areas that are mainly indicated in end term reports, which is consistent with the primary stakeholders of the programme: policy makers and HTA professionals. A smaller number of project results will be used in education, e.g. master classes and HTA courses at universities, and clinical practice.

2.4 Conclusions

Based on the results of this evaluation, it can be concluded that this programme has yielded favourable results with respect to the aforementioned areas of evaluation. The evaluation reveals that stakeholders are sufficiently involved, projects were distributed equally across the major themes, quality assurance was maintained, HTA methodology is developed and improved and dissemination to different sectors (research, policy, practice and education) was adequately performed and facilitated.

Taken together, the HTA methodology programme, although not yet completely finished, has already made a considerable boost in HTA research in The Netherlands which can be applied in drug efficiency research and decision-making on the efficient use and reimbursement of drugs but also in other fields of efficiency research and decision making. The fact that proposals did not have to be related to a clinical trial as was necessary in a previous programme, resulted in a broad-spectrum of HTA research being carried out. The results of the majority of the finalised projects filled knowledge gaps in HTA methodology that can be used in the revision of ZIN guidelines, i.e. the pharmaco-economic guideline, the guidance for outcome research and the cost manual. The programme also has contributed to a good international reputation of Dutch HTA methodology research as evidenced by prominent presence of Dutch researchers at HTA congresses (e.g. ISPOR) , successful acquisition in international funding (e.g. Horizon 2020) and the involvement of Dutch researchers in the technology appraisals of the National Institute for Health and Care Excellence (NICE) in the United Kingdom.

However, the majority of the projects resulted in a need for further research, as both the existing research questions ask for more research and new research questions have arisen, indicating the need for continuation of the HTA methodology programme. Furthermore, the HTA budget was insufficient to fund all HTA projects qualifying for the criteria in the call texts as already observed in the Midterm self-evaluation report. Finally, as in the current HTA programme the link with the EODP was mandatory, the programme committee noticed that projects were regularly narrowed in this respect, while a wider focus would have been interesting. Also, many opportunities for HTA research beyond pharmaceutical drugs, could not be addressed.

3. Design and execution of the HTA methodology programme

3.1 Programme design

In August 2007, the Ministry of VWS approved the execution of the EODP with an allotted budget of € 24.05 million. Of this budget, €6.4 million was designated for the HTA methodology programme, under the condition that the programme text and design would be developed by ZonMw and submitted to the Ministry of VWS for approval. The programme design was developed by an advisory committee organised by ZonMw, consisting of various HTA experts based in the Netherlands. The programme text was subsequently drafted by ZonMw and approved by the Ministry in 2008.
The preeminent goal of the HTA methodology programme was to develop and improve HTA methodology for application in drug efficiency research and decision-making on the efficient use and reimbursement of drugs. Accordingly, funded projects should lead to new or improved HTA instruments that can be used for outcomes research. Projects were selected based on criteria consistent with the project goals: projects should develop or improve HTA methodology, results must be useable in drug efficiency research, and research should lead to new insights or instruments supporting decision-making in regards to drugs. Furthermore, results should be relevant to the ZIN and its revision of pharmaco-economic guidelines.
In order to meet programme goals, calls for proposals were guided by setting themes and priorities for each call. Only applications that focused on one of these predetermined themes were accepted. The themes were subdivided into topics; for example, the overarching theme of the first and second calls was based on the 'Guidance for Outcomes Research' report of ZIN[9] which details important knowledge gaps to be addressed in HTA. The subtopics within this theme were as follows: *Design & Analysis*, *Data on Costs*, *Clinical Data*, *Clinical Practice*, and *Normative Interpretation of Results*. For the third call, members of NVTAG were consulted in order to incorporate the input of a variety of HTA professionals. From the third round onwards, the themes were *Costs & Outcomes, Decision-making* and *Design & Analysis*. The option was also granted to allow researchers to submit research into other areas apart from the pre-designated themes (theme: *Other Areas*), in order to ensure the inclusion of as many ideas as possible. In this report projects are categorized in the themes used from the third round onwards; projects of the first two rounds were recategorized into these themes.

3.2 Programme committee

The ZonMw Board of Directors set up a programme committee comprised of national research experts from various backgrounds, including clinicians, pharmacists, epidemiologists, and HTA experts. Furthermore, the Ministry of VWS and ZIN, have non-voting members within the programme committee.
This committee handles the executive management of both parts of the EODP, including the HTA methodology programme. Among the tasks mandated to the committee are the finalisation of the programme information documents and calls for proposals, the assessment and ranking of project proposals, the monitoring of funded projects throughout their lifetime (including knowledge production and implementation), and the overall interim and final evaluation of the programme.
According to the ZonMw Code of Conduct regarding Conflict of Interests HTA experts were not allowed to comment on applications from their own institutions or applications in which they were involved. They could not be present for the discussion, and they were not allowed to vote for or prioritise a complete set of applications in which they had a conflict of interest.
In Appendix 1 an overview of the members of the HTA methodology programme committee is given.

3.3 Programme execution

3.3.1 Programme logistics and call requirements

According to ZonMw procedures, call texts and their corresponding requirements were published on the ZonMw website and in the *Mediator* (the ZonMw magazine). Conditions applied throughout the programme included several elements. Proposals must fulfil general ZonMw Grant Terms and Conditions. In addition to this, research budgets must not be in excess of €125,000, and project duration must not exceed 24 months. Also, in alignment with project goals, the research must connect to one of the themes or priorities mentioned in the call text, and study results must be relevant for research and decision-making on the efficient use of drugs.

[9] http://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/publications-in-english/2008/0812-guidance-for-outcomes-research/Guidance+for+Outcomes+Research.pdf

3.3.2 Calls for Proposals

The HTA methodology programme commenced its first call in 2008, with a total of six calls. A total number of 193 project ideas were submitted throughout these calls, of which 190 passed the initial acceptance phase. Of these submissions, 105 were expanded to full proposals, of which 53 projects (approximately 50%) granted funding. Figure 3.1 depicts the ratio of the submission of ideas, submission of proposals, and projects funded across the six calls.

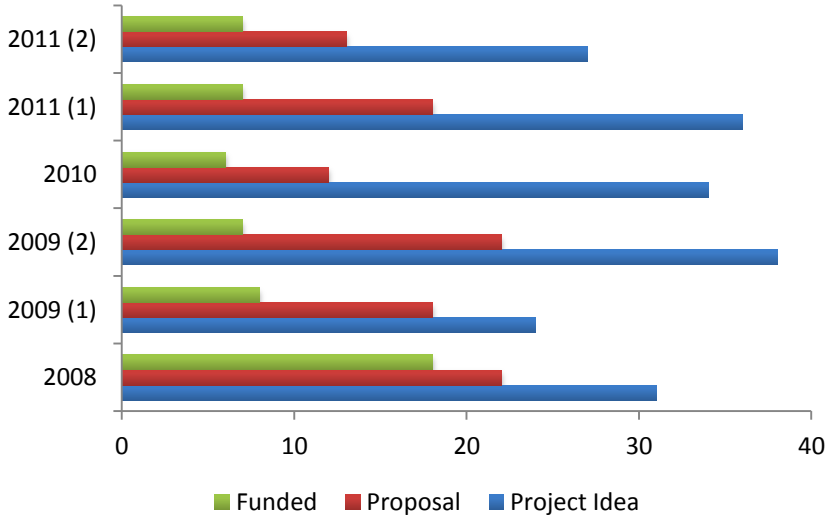

Figure 3.1 Submissions received during calls for proposals (2008-2011)

Funded projects were distributed evenly across the three themes: Cost & Outcomes (19 projects), Decision Making (16 projects), and Design& Analysis (18 projects).

3.3.3 Programme Financing

As previously mentioned, €6.4 million was available at the start of the programme for the funding of HTA projects. For the first call for proposals €2.2 million was allotted to give an initial boost; all proposals that met programme criteria received funding. The remaining budget was distributed among the other calls. The total amount of funding allotted per call as well as the amount paid per call upon the finalisation of project selection (for projects that are not yet finished the assigned budget is used) are stated in *Table 3.1.*

Call	No. of funded projects	Total budget (€)	Total paid (€)
1	18	2,051,765	1,948,216
2	8	931,259	920,037
3	7	862,379	853,439
4	6	732,420	721,534
5	7	864,348	864,348
6	7	873,149	873,149
Total	53	6,315,320	6,180,723

Table 3.1 Total budget assigned per call and total funding paid

Table 3.2 lists funding allocations across various institutions in the Netherlands. The institute for Medical Technology Assessment (iMTA) of the Erasmus University Rotterdam (EUR) was very successful in acquiring funding for their projects, as projectleader. This could be related to the size of this institution compared to the other academic departments, and its early involvement in outcome research with expensive drugs.

Institution	No. of funded projects	Total funding awarded
AMC	1	124,979
EUR/Erasmus MC	20	2,321,202
LUMC	7	866,717
MUMC	6	647,290
RIVM	1	124,489
UMCN	3	374,242
UMCU	5	621,167
UMCG	6	749,968
Twente University	2	242,473
VU Amsterdam	2	242,793

Table 3.2 Total funding per institution

3.4 Assessment procedure

The assessment was organised and executed according to ZonMw guidelines.[10] To be selected projects had to meet the programme goals and priorities of the call. Applicants who had received positive advice for their initial project idea were typically also given recommendations on how to improve and strengthen their application for the development of a full proposal. In some cases, applicants who had submitted proposals that were almost identical (or applications which would be strengthened by being combined) were advised to contact the programme secretariat to discuss the feasibility of collaboration. Applicants were required to react on committee advice, questions, and feedback by sending in a detailed written account demonstrating how they had changed their application according to committee remarks. This helped to improve the quality of funded projects as well as give project leaders the opportunity to reflect on the comments of the programme committee. Applicants were given the opportunity to appeal the decisions of the programme committee regarding their applications. Only once during the programme a project leader objected the decision of the programme committee.
Of the 53 funded projects, 25 were funded under conditions and only when these conditions were met the decision to fund the project was confirmed. In 18 of these 25 projects the budget had to be adapted or clarified, and for 13 projects clarifications to the research strategy and study plan were requested. These conditions were also intended to improve the quality of funded projects.

3.5 Project monitoring

To improve quality, all projects are subject to monitoring activities from the moment of funding.

3.5.1 Start-up support

Funded projects were required to start within six months following the awarding of the grant; this deadline could be extended in exceptional circumstances. Eight projects requested and received approval for extensions of the 6-month start-up period. A further four projects had delays beyond 6

[10] Annex 2: ZonMw Summary Assessment Procedure

months of which ZonMw was not informed. Among the reasons provided by researchers warranting the need for project delay, the most predominant was the lack of availability of suitable research staff.

3.5.2 Mid-term reports

All projects with a duration of 24 months required a mid-term report after 12 months. For the majority of projects the progress report was directly approved, five mid-term reports were revised.

3.5.3 End-term reports

An end-report had to be submitted within four months of project completion. The programme committee determined that, for every end-term report, at least two HTA experts in the committee (typically those who also reviewed the application during the call phase) were required to review and provide approval.
At present, 38 reports have been approved. In 27 cases the committee has requested additional information or delivery of promised instruments by research teams. Furthermore, on 6 occasions research teams were required to provide new end-term reports due to inadequate information in the initial submitted report. Thus, the additional work and contribution of the programme committee resulted in further substantiation of the performed research.
Of course, the comprehensive nature of this procedure placed added strain on the workload of HTA methodology programme committee members. Despite this, in almost all cases, the review and feedback from committee was received, and the average time taken to approve end-term reports was 20 weeks. This period includes both the time of the program secretariat and committee members for review and the time needed by research teams to provide any additional information, promised instruments and new end-term reports.

3.5.4 Additional progress monitoring

Monitoring of projects outside the aforementioned reporting procedures is based solely on contacts made to the secretariat by project leaders. Most changes throughout projects concern alterations in budget and requests for project extension.
In total, 29 projects received approved extensions. The minimum prolongation was one month, while the maximum was 24 months. The most common causes of research prolongation were issues or events involving the research staff (for example, health issues, maternity leave or replacement of team members), study protocol (for example, analysis taking more time than expected), or implementation activities.

4. Results of the HTA methodology programme and their implementation

4.1 Project results

To date, 38 projects have been finalised, 14 are ongoing and one project was stopped prematurely due to issues with research staff. Of the finished projects, 28 projects (75%) fully delivered the results they aimed to produce. Ten projects partially delivered the promised results due to various circumstances; however, these projects nonetheless produced valuable knowledge.

Various HTA instruments for use in practice were developed so far (see Appendix 2 for an overview). The 21 instruments developed so far consist of questionnaires, models and practical tools. In the area of Costs & Outcomes, tools were developed in previously unaddressed areas such as measuring the quality of life in patients with dementia (this project won the Quality Prize in 2012). In the area of Design & Analysis, knowledge gaps pertained to policy development for the conditional reimbursement of expensive and orphan drugs; for example, a project addressed how to utilize n=1 studies in reimbursement decisions. For the theme of Decision-Making, projects addressed gaps such as models for the determination of the value of QALY gains to aid in the Dutch decision-making model and a checklist to assess whether the HTA is generalizable to the decision context is developed. Next to the development of new instruments, existing methods were investigated further such as Bayesian analyses, value of information analyses, meta analysis methods, and utility mapping. Furthermore, new theoretical insights into methodological issues regarding efficiency research and decision making were obtained, among which discounting in economic evaluations, equity weights, marginal utility of health, and societal preferences. In Appendix 3 a comprehensive overview of the results is presented for each project.

Although substantial results have been achieved within the current programme, in the majority of the projects (67%) researchers indicated that further research is necessary because outcomes of the relative short termed (24 months) projects may have been not conclusive yet and/or results may have revealed new research opportunities.

4.2 Communication and implementation of results

A Communication and Implementation Plan (CIP) is a document specifying the actions and efforts necessary to insure optimal communication towards different stakeholders and maximisation of the implementation of project results. All ZonMw programmes require a CIP; the CIP for the HTA methodology programme was written by experts of the Institute for Medical Technology Assessment (iMTA) on commission by ZonMw, and given final approval by the HTA methodology programme committee in 2010. Discussions on the implementation activities and budget were finalised in October 2012 by the programme committee. The development of an extensive e-platform for guidelines and methodologies was cancelled due to expense and competition with larger, more international databases; instead, emphasis was placed on other activities such as Dissemination and Implementation Impulses (VIMPs) and HTA symposia. The idea for a reference book was also rejected due to the rapid development of HTA methodology, which would quickly warrant the book out-dated by time of publishing. This has led to a revised version of the CIP.[11]

In the programme budget a total of €1.2 million was available for communication and implementation activities of the EODP; of this amount €500,000 was allocated for the HTA methodology programme. CIP activities can be divided into communication and implementation at project and programme level (that is, the HTA methodology programme). These latter tasks are executed or commissioned by ZonMw in order to support the dissemination or programme results.

[11] Annex 5: Revised Communication & Implementation Plan (2014)

4.2.1 Project-level Communication and Implementation Activities

A frequent way of communicating study results is publication of the results in research reports or scientific journals and presentation at scientific congresses. *Table 4.1* lists the overview of the knowledge output currently reported to ZonMw. For ongoing projects an estimate of output is based on the mid-term reports.

Knowledge Output	Costs& Outcomes	Decision Making	Design & Analysis	Total
Publications	23	9	37	69
Papers in preparation	20	13	14	47
Research reports	1	0	3	4
Dissertations	1	1	2	4
Presentations	31	22	24	77
Workshops/Masterclasses	0	1	4	5

Table 4.1 Knowledge output

All results of finalised projects have been published or are in preparation for publication in scientific journals. Journals in which the results are published include Value in Health, Quality of Life Research, Medical Decision Making, Health and Quality of Life Outcomes, Pharmacoeconomics, Pharmacoepidemiology and Drug Safety, and Health Policy.
Results have also been presented at different national and international scientific congresses, including NVTAG, VGE, Lola-HESG, iHEA, ECHE, HTAi, and ISPOR.
Areas in which the results can be used according to the information of the end-term reports (or the mid-term report when the project is ongoing) are most frequently policy (40 projects) and research (49 projects), but also in education (7 projects) and clinical practice (10 projects)

4.2.2 Programme-Level Communication and Implementation Activities

ZonMw led many of the dissemination and implementation activities at the programme level. These activities include website publications, facilitation of revision of ZIN guidelines, the organisation of project leader meetings and theme discussions. Furthermore, the programme was presented at a poster meeting of the Society for Medical Decision-Making Congress (SMDM) Conference in Washington in November 2011. Finally, a publication for the general public on the results of the programme will be prepared.

Website publications
All funded projects are published on the ZonMw website in full.[12] At the start of each study, a summary of project intent and expected results are published. Upon project completion, the results and research products are published, as well as relevant news items and publications. In addition, ZonMw has also published a flyer on the website giving an overview of all funded HTA methodology projects at ZonMw from 2004 onwards.[13]
Furthermore, information and news regarding the HTA methodology programme are regularly published in the newsletter of the Rational Pharmacotherapy programme, as well as a special newsletter dedicated solely to HTA methodology in 2013.[14]
Up until October 2013, regular news emails were also sent to a list of interested persons. These emails were used to disseminate information on new publications and finalised projects. This information has now been incorporated in the *Mediator* (the official ZonMw magazine).

Dissemination and Implementation Impulse (VIMP)
VIMPs are utilised to facilitate additional communication and implementation activities. A VIMP is a grant of up to €50,000 which funds additional communication and implementation activities for a maximum duration of 12 months. VIMPs can be suggested through theme discussions, by independent project leaders and ZonMw implementation discussions to enhance the uptake of study results. The programme committee is informed and decides whether or not the project leader can be invited to submit a VIMP proposal; in some cases, ZonMw can also invite several project leaders to

[12] http://www.zonmw.nl/nl/programmas/programma-detail/doelmatigheidsonderzoek-farmacotherapie/hta-methodologie/
[13] www.zonmw.nl/nl/themas/thema-detail/doelmatigheid/hta-studies/
[14] www.zonmw.nl/nl/nieuwsbrieven-20/geneesmiddelen/geneesmiddelen-special-hta-methodologie/

submit a joint-VIMP proposal, in which case the maximum grant can be increased when activities warrant a higher budget. The ZonMw Management Team makes the final decision on whether or not to award a VIMP grant. At present, six VIMPs have been granted on Bayesian analyses, Value of Information analyses, outcomes beyond the QALY, execution of N=1-studies, the value of QALY gains, and a structured overview of the costs of various types of research in health sciences. The total amount allotted to the VIMPs is €241,070.

ZIN guidelines revision

ZIN is revising the Dutch guidelines for pharmaco-economic research i.e. the pharmaco-economic guideline, the guidance for outcome research and the cost manual. The aim of the revision is a new guideline bringing the existing guidelines together, which is consistent and broadly applicable in health economic research. In 2012,following a tender procedure, ZIN and ZonMw commissioned the MUMC to perform research into the results of the 24 finalised projects funded by the HTA methodology programme of the EODP. The aim of this research was the extraction of relevant information for the revision of ZIN guidelines. In 2015, this research was updated based on recently finished HTA projects. The results of the HTA methodology projects frequently indicated revision of the pharmaco-economic guideline or guidance for outcome research. In a majority of the projects also further research was indicated. A smaller number of projects had results that indicated a revision of the cost manual, see *Table 4.2.*

CVZ Guideline	*40 projects*
Pharmocoeconomic guideline	
Revision indicated	5
Research indicated	8
Both revision and research indicated	15
No revision nor research indicated	12
Guideline outcome research	
Revision indicated	7
Research indicated	8
Both revision and research indicated	15
No revision nor research indicated	10
Manual cost research	
Revision indicated	3
Research indicated	2
Both revision and research indicated	5
No revision nor research indicated	30

Table 4.2 Number of projects indicating guideline revision and/or research

As the HTA methodology programme was founded on these guidelines and solving their knowledge gaps, it can be concluded that the programme succeeded in this respect.

Topics for which results of the HTA methodology projects of the EODP programme *only* indicated revision of the guidelines are

- Methodology for the assessment of clinical effectiveness
- Framing of an economic evaluation
- Discounting
- Place and value of Bayesian analysis
- Momentary experienced utility
- Tailoring the period of conditional reimbursement
- Sample size calculation

Topics for which results of the HTA methodology projects of the EODP programme *only* indicated further research are

- Valuation of patient time
- Measurement and estimation of states worse than dead
- Measurement of well-being
- Composite time-trade off
- Best-worse scaling to determine patient preferences
- Reference prices
- Instrumental variable analyses
- Willingness-to-pay threshold

Topics for which results of the HTA methodology projects of the EODP programme indicated revision of the guidelines and further research are

- Broadening the evaluative space to aspects other than health
- The place and value of patient preferences
- Double counting issues related to the incorporation of spill-over effects in informal caregivers and significant others
- Utility mapping of specific instruments to generic preference based instruments
- Time preferences in time trade off
- Uncertainty (Bayesian analysis, meta-analysis, value of information analysis, acknowledging heterogeneity, censoring)
- Indirect medical costs
- Confounding bias
- Use of registries
- Generalisability and extrapolation of trial data

Project leader meetings
Project leader meetings were organised for the dissemination of information and new knowledge among HTA professionals, to facilitate networking between researchers and stakeholders, and to support implementation. The meetings, which were open to all interested parties, were announced via the ZonMw website, newsletters, and emails. During these meetings, project leaders and researchers were given the opportunity to present their study and results, and also stakeholders such as HTA experts from pharmaceutical companies and ZIN delegates were allotted time to give presentations.

Project Leader Meeting	No. of presentations	No. of panel discussions	No. of attendees (approx.)
28 January 2010	28	1	70
12 September 2011	7	2	70
16 April 2013	9	1	60
8 December 2014	11	2	60

Table 4.3. Overview of Project Leader Meetings

The first project leader meeting was held in January 2010 in joint effort with NVTAG. The programme contained two plenary presentations, parallel sessions on the research themes, and a forum discussion. A second project leader meeting was held in September 2011 (also in cooperation with NVTAG).[15] The third meeting was held in April 2013, with professor Allan Wailoo (UK) as guest speaker presenting on the topic ‘Developing the NICE Guide to the Methods of Technology Appraisal:

[15] www.zonmw.nl/hta2011

The View from Academia'.[16] In December 2014 the project leader meeting focussed on internationalization. Several examples of international collaboration in methodology projects were presented and a 360° view of international grant programs was given. Each meeting had over 60 attendees.
Table 4.3. outlines the events of the four project leader meetings. The large number of presentations, panel discussions, and attendees from various fields relevant to HTA is crucial to the dissemination and implementation of project results, as well as the networking of parties in HTA for the furthering of HTA methodology research.

Theme discussions
The theme discussions are a means by which programme themes are examined in context with its corresponding projects. Academic researchers, researchers from the pharmaceutical industry, and members of the programme committee are typically invited to these discussions. This allows the synthesis of new knowledge, the dissemination of results amongst different researchers within a theme, as well as the incorporation of new methodologies into their work procedures. These discussions also facilitate consensus on results, as well as future research implications. If additional research and/or communication and implementation activities are deemed necessary, ZonMw can plan a VIMP in accordance with the required additional activities. For example, the theme discussion in 2013 focused on 'Value of Information'; this discussion led to a combined VIMP for four projects, which aimed to write a chapter for the Guideline Outcome Research on the use of Value of Information (VOI) analysis. Furthermore, a panel discussion on the same topic was organised at the November 2014 European ISPOR conference. Another theme discussion was held in 2014 on the topic 'Quality of Life'. For this meeting also researchers of the Netherlands Organisation for Scientific Research (NWO) programme "Quality of Life and Health" were invited. Based on the outcome of the meeting the committee decided not to request a combined VIMP comparable to the VOI VIMP as the content of the projects was too diverse. Instead, ZIN and ZonMw commissioned the iBMG to prepare a chapter on Quality of Life for the ZIN guidelines, together with a projectteam in which expert groups from various centers are involved. This project started in 2015.
Table 4.4 summarizes the number of ZonMw-led communication and implementation activities performed as of December 2014. The ZonMw website remains the main instrument of communication, while VIMPs and project leader meetings are also vital to knowledge-sharing and implementation of project results.

Communication and Implementation Activity	No. of activities
Projects on the ZonMw website	53
Poster presentations at international congresses	1
Project leader meetings	4
ZIN guidelines commissions	2[1]
Flyers	2
Theme discussions	2
Panel discussions ISPOR	2[2]
VIMPs	6

Table 4.4 Communication and implementation activities at programme level (until December 2014)
[1] *This commission between ZIN and ZonMw continues in 2015*
[2] *These panel discussions are based on the ZIN guideline commission and the VIMP on VOI analysis*

[16] www.zonmw.nl/hta2013

Appendix 1. Overview of the members of the HTA methodology programme committee

Voting members
Prof. dr. W.G. van Aken, chairman (from start)
C.F.R.M. van Bezooijen, MD, patient representative (from start)
Prof. dr. W.B.F. Brouwer, health economics (from start)
Dr. T.L. Feenstra, health economics (from July 2010)
Prof. dr. F.M. Haaijer-Ruskamp, pharmaco-epidemiology (from start till April 2010)
Prof. dr. J.M.W. Hazes, rheumatology (from start till February 2009)
Prof. dr. Y.A. Hekster, pharmacology (from start)
Dr. W. B. van den Hout, health economics (from January 2009)
Dr. M.A. Joore, health economics (from start)
Prof. dr. P.C.M. van de Kerkhof, dermatology (from May 2009)
Dr. C. Kramers, internal medicine/pharmacology (from start till May 2012)
Prof. dr. D. Richel, medical oncology (from May 2009)
Dr. J.H. Schornagel, oncology (from October 2008 till March 2009)
Prof. dr. A. Steenhoek, medicinal policy (from start till June 2014)
Prof. dr. J.L. Severens, health economics (from start till June 2008)
Prof.dr.B.H.Ch. Stricker, pharmaco-epidemiology (from start)
Prof. dr. E.E. Voest, oncology (from start till April 2009)

Non-voting members
Dr. W.G. Goettsch, ZIN (from start)
Drs. H. Kooijman, VWS (from start)

Programme officers ZonMw
Dr. S.J. de Visser (from start to April 2008)
Dr. B.E. Vingerhoed-van Aken (from October 2007 till November 2011)
Dr. L. Terhell (from August 2008 till March 2013)
A. van Sonsbeek (from December 2011)

Appendix 2. Developed instruments in the HTA methodology programme

Project Number	Developed tool
152002004	Micro-simulation model to determine the optimum treatment for patients with severe haemophilia
152002007	Checklist to frame a health technology assessment study.
152002009	Modular instrument for the measurement and valuation of informal care
152002010	Correction model for discounting health state valuations derived with TTO.
152002013	Algorithms (syntax) and manuals for three disease specific questionnaires (HAQ; EORTC-QLQ-C30; MSIS-29) to 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
152002020	Adapted versions of the Experience Sampling Method and the Day Reconstruction Method to measure the momentary experience of mood, physical complaints, and overall health.
152002021	Checklist to help national guideline authorities to formulate comprehensive recommendations with regards to acknowledging patient heterogeneity in economic evaluations
152002022	PAID 2.0 tool to calculate indirect costs within health care, description of the technical background and a manual.
152002024	The developed instrument called the ‘Dementia Quality of Life Instrument’ classifies patients on the following domains: ‘physical health’, ‘self-care’, ‘social functioning’, ‘mood’, ‘memory’, and ‘orientation’.
152002025	Prediction model for extrapolating treatment effects as found in phase II/III clinical trials in Rheumatoid Arthritis daily clinical practice.
152002026	Guideline document on how to use predictive markers
152002027	Software (in R) to adjust for informative censoring by using G- computation
152002028	Two toolkits that aid potential users of the Tailored Medicine Inventory and the Generic Medication Evaluation to develop these questionnaires for a specific group of users
152002030	Blueprint for a N=1 trial database
152002031	Real Options Method: an instrument that allows setting the length of the period for evidence development by balancing costs and benefits of further evidence gathering. It uses information on prevalence, incidence, treatment duration and other relevant parameters.
152002032	Method to comprehensively value time of people not participating in the labour market
152002034	An algorithm was developed to calculate time-dependent valuations for the Better than Dead method
152002039	An application for eliciting TTOs was developed; a user support is offered a.o. in the form of training and a manual that describes the use of the application
152002044	For the EQ-5D-5L a model was defined that predicts the values of the states for which there are direct observations and, thus, can be used to interpolate values for the states for which no direct observations exist. The tariff predicts values for the 3125 health states of the EQ-5D-5L.

Appendix 3. Overview of results of projects funded in the HTA methodology programme

Project Number	Title	Theme	Objective	Results
152002001	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	Design & Analysis	To test the usefulness of a Bayesian approach to analysis and synthesis of data in guiding health care policy decisions	Bayesian methods are very useful for evidence synthesis. Moreover, Bayesian outcomes have interpretational advantages for policy makers.
152002002	Updating parameters of decision-analytic cost effectiveness models: a systematic comparison of methods	Design & Analysis	To compare fixed end random effect methods of meta-analysis	When all trials are randomly drawn from the same underlying population (direct comparisons) the bias and mean absolute deviance is generally smaller for the FE methods than for the RE methods. The indirect comparisons perform less well with a greater bias and lower statistical power.
152002003	Further exploration of the appropriateness of the well-being valuation method for monetary valuation of informal care: what is measured?	Costs & Outcomes	Development of the well-being valuation methodology for the monetary valuation informal care	The results substantiate the validity of the methodology.
152002004	Treatment of severe haemophilia: Optimal data-usage for optimal treatment strategies	Design & Analysis	To combine information on different treatment strategies for haemophilia and to build a model to assess the optimum treatment strategy	A micro-simulation model has been delivered but is very disease specific. Further research is required to make the model applicable for cost-effectiveness research and to compare this model to already existing models.
152002005	Prioritizing and designing outcomes research: the role of value of information analysis	Decision Making	To study the importance of formal VOI analysis when considering conditional reimbursement	More insight in the use of VOI analyses. Conclusion was that PSA/EVPI should always be performed but EVPPI is not always necessary
152002006	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	Decision Making	To develop and apply methodologies for the purpose of supporting reimbursement decisions: VOI and Bayesian statistics	A literature review in cost-effectiveness of antifungal prophylaxis in neutropenic patients; insight into MTC and VOI analyses.
152002007	A framework for real world economic evaluation of pharmaceuticals	Decision Making	To develop a framework for real-world economic evaluations that will be used by scientists and decision makers.	Checklist developed and used in a case of adjuvant therapy of trastuzumab
152002008	Discounting Health Effects: further analysis of its rationale and the theoretical & empirical implications	Design & Analysis	To further develop and to provide practical implications for discounting in economical evaluations	The project shows the relevance and validity of differential discounting which presently is only done in The Netherlands and Belgium
152002009	The inclusion of informal care in health economic evaluations: developing a standardised, modular instrument and user manual including the CarerQol	Costs & Outcomes	To establish a modular instrument for the measurement and valuation of informal care	A modular questionnaire is developed. Also a manual is generated, which provides users of the questionnaire with background information. In this manual, a tariff for different caring states described by the CArerQol-7D instrument is included.

Project Number	Title	Theme	Objective	Results
152002010	Correcting health state valuations derived with TTO for discounting	Design & Analysis	To research whether TTO is distorted by discounting (when people value their present health higher than future health)	Correcting TTO scores is influential and the Direct Method is a feasible method for this correction. Correction factors have been established. The results improve the TTO methodology
152002011	Equity weights for QALYs	Decision Making	To evaluate and to operationalise the concept of proportional shortfall by deriving the corresponding QALY weights	The results demonstrated that proportional shortfall by itself does not adequately capture societal preferences
152002012	Feasibility of cancer registries as a Health Technology Assessment tool in pharmacotherapy	Costs & Outcomes	To define the feasibility and qualifications of a dedicated cancer registry to be usable for estimating (cost)effectiveness of oncological drugs	The linkage with an external database was feasible. It was examined how a cancer registry can be improved and which variables are required to perform a cost-effectiveness analysis. It was found that the cohort in the external database was too small to monitor the effectiveness and safety of new cancer treatments.
152002013	Quality of life in expensive drugs: deriving preferences in absence of generic health state valuations	Costs & Outcomes	To valuate three disease specific questionnaires to generate values that can be used in economic evaluations: HAQ; EORTC QLQ-C30 and MSIS-29. Also the methodologies used to generate the disease specific utilities will be validated by comparing them to the EQ-5D values.	Mapping seems to be the preferred strategy to derive values when generic preference based measures have not been administrated.
152002014	Advanced value of information methods to health technology assessment of expensive medicine and orphan drugs	Design & Analysis	To develop a dynamic Bayesian VOI model to inform decision making about reimbursement and research funding concerning expensive and orphan medicine	Project stopped prematurely; a comprehensive literature study has been performed and interviews were held
152002015	From disease specific health status to generic utility. Methods to improve piggy-back utility analysis in controlled clinical trials	Costs & Outcomes	To compare a disease-specific and generic questionnaire and estimate utilities for the disease specific questionnaires	Cancer vignettes have been developed consisting of 8 items of the QLQ-C30
152002016	The marginal utility of health: direct and indirect valuation of EQ5D differences	Costs & Outcomes	Aim of the study is to analyse whether the difference between both types of research (diminishing versus increasing marginal utility) can be attributed to framing (change versus state) and/or to perspective (self versus other).	There were no differences in valuation of health improvements between the self perspective and the others perspective. However, in all analyses, health improvements were consistently considered more valuable in good health than in poor health. These results question the robustness of the foundations for using differential cost-effectiveness thresholds.
152002017	Confounding in real-life cost-effectiveness studies: assessing the validity and efficiency of different correction techniques	Design & Analysis	To investigate how different confounding bias correction techniques perform in terms of validity, reliability, coverage and statistical power in the setting of observational cost-effectiveness research, with a focus on the list of expensive medicines.	Knowledge on the effect the choice of correction technique on the analysis of observational data. A decision support tool was developed.
152002018	Productivity costs in cost-effectiveness studies on expensive drugs	Costs & Outcomes	To find out whether economic evaluations on expensive drugs include productivity costs; in which case these costs should be included and how the in- or exclusion affects cost-effectiveness outcomes.	Insights in the implications on cost-effectiveness outcomes that is caused by the in- or exclusion of productivity costs in the analysis. A simple decision tree was developed.

Project Number	Title	Theme	Objective	Results
152002019	Societal preferences for basic health insurance in the Netherlands	Decision Making	To assess the relative importance Dutch citizens attach to the different characteristics of health interventions.	These insights are studied for age, gender, socioeconomic status, disease severity, number of people with the disease, health gain due to intervention and chance of treatment success. The relative importance is assessed using the Best Worst Scaling (BWS) method and the Willingness to Pay method (WTP). The relative importance differed between the two methods.
152002020	The Q in the QALY: exploring new methods	Costs & Outcomes	To investigate the potential use and value of experienced utility, as measured by the experience sampling method (ESM) and the Day Reconstruction Method (DRM), in the economic evaluation of health care.	The ESM and DRM were adapted to measure the momentary experience of mood, physical complaints, and overall health (experienced utility). The feasibility of the ESM and DRM was found to be satisfactory. Both the ESM and DRM showed a three-factor solution on a principal components factor analysis: positive affect, negative affect, physical complaints and overall health. Conclusions: Experienced utility differs from decision utility.
152002021	Acknowledging heterogeneity in Health Technology Assessment to improve efficient use of pharmaceuticals	Design & Analysis	To develop guidance on how to handle patient heterogeneity within economic evaluations and decision making upon drug reimbursement	Insight into how to acknowledge patient heterogeneity. Patient heterogeneity can be acknowledged in economic evaluations during the design, analysis and presentation phase. A checklist was developed which may help guideline authorities to formulate their guidance on acknowledging patient heterogeneity in economic evaluations.
152002022	Estimating indirect medical costs and its associated uncertainly	Costs & Outcomes	To a) quantify sources of uncertainty surrounding indirect medical costs (IMC) b) to develop a tool that enables HTA researchers to include estimates of indirect medical costs including estimates of uncertainty in a standardized manner in economic evaluations.	Main results are a) IMC will be underestimated if one does not take into account the future rise in health care expenditures b) the main source of uncertainty surrounding estimates of IMC is how health care costs develop in the future. Uncertainty surrounding IMC is underestimated if one does not model the uncertainty surrounding future time trends in health expenditures. The above mentioned insights are incorporated in the software PAID 2.0.
152002023	Significant others in economic evaluations	Costs & Outcomes	To test whether respondents in Health State Valuation using Time Trade Off include 'significant others effects' and how this affects trade-offs. Moreover, it tests the consequences of explicit instructions to include/exclude 'significant others effects', as well as explicit information on these effects.	The results imply that the effects on significant others already seem to be partly captured in health state valuations (and subsequently the QALY). The inclusion of significant others effects potentially results in double counting if significant others effects are also measured separately.
152002024	Quantifying health status in dementia	Costs & Outcomes	To develop a dementia-specific index instrument. Such an instrument classifies people on a number of domains and has specific weights for each level of the domains which allows a single meaningful value to be attached to each individual health state.	The developed instrument called the 'Dementia Quality of Life Instrument' classifies patients on the following domains: 'physical health', 'self-care', 'social functioning', 'mood', 'memory', and 'orientation'. Based on weights derived from the general population an algorithm was developed that allows to attach meaningful values between 0 (death) and 1 (perfect health) to each potential DQI health state.
152002025	Novel modelling approaches to reconcile the paradigms of randomization and representativeness in (cost-) effectiveness analysis: The case of Rheumatoid Arthritis	Design & Analysis	To study 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)	Patient characteristics and treatment effects found in pragmatic RCTs can differ substantially from clinical practice. A prediction model was developed but not yet validated.

Project Number	Title	Theme	Objective	Results
152002026	Evaluating putative predictive markers in randomized clinical trials of pharmaceuticals	Design & Analysis	To develop a sound strategy for including evaluations of potentially predictive markers in the design phase of pharmaceutical trials.	A systematic literature review on designs for the evaluation of predictive markers (treatment selection markers) was performed. A guideline document was drafted in which a number of considerations to evaluate the effects of using one or more markers as predictive markers (treatment selection markers) were offered.
152002027	Informative censoring in time-to-event data and consequent bias in HTA	Design & Analysis	To assess properties of the Inverse Probability of Censoring Weighting (IPCW) and other methodology that are used in clinical trial data with a cumulative survival endpoint, and their implications on the estimates of the cost-effectiveness ratio.	The smallest bias is achieved by using G-computation based on a conditional model in which covariates are averaged out by a "plugin"-estimator. Software has been developed in R.
152002028	Patient preferences for and experiences with chronic medication use: development of two web-based instruments	Costs & Outcomes	To measure experiences and preferences with medication in a standardized way.	The research has provided insight into how users of different groups of drugs experience treatment and how they weigh the pros and cons of these treatments Patients weigh the pros and cons for the different groups of medicines different. There are also separate determinants found for intentional and non intentional adherence. Two 'toolkits' are available that aid potential users of both the Experiences with Medication Questionnaire and Generic Medication Evaluation to develop these questionnaires for a specific group of medicine users.
152002029	Combining N-of-1 trials to estimate population clinical and cost-effectiveness of drugs using Bayesian hierarchical modelling. The case of Mexilitin for patients with Non-Dystrophic Myotonia	Design & Analysis	To explore the validity of N=1 trials in producing evidence of clinical and cost-effectiveness of drug treatments for patients with rare diseases.	No results available yet.
152002030	From rationing to rationality: an n-of-one trial service for off-label medicines for rare (neuromuscular) diseases	Design & Analysis	To develop an 'n-of-1' trial service, integrated in the Dutch health care (assessment) system. The purpose is to promote equitable pharmaceutical care for patients with rare diseases and to generate evidence on the efficacy of promising, off-label drugs.	N-of-1 trials provide an opportunity to conduct effectiveness research in a population in which it is difficult to conduct research due to small numbers of patients. It is currently premature set up a national n-of-1 trial service. Further questions about the robustness of the aggregated results of n-of-1 trials compared to results obtained through more familiar and established research designs such as RCT's will need to be addressed first, as well as remaining questions about the size of the patient population for which an n-of-1 trial service could provide 'personalised medicine' (perhaps both for rare disease patients and patients with more common chronic diseases). Furthermore, Dutch researchers, clinicians, pharmacies and health authorities should become more familiar with the n-of-1 trial design. A blueprint was developed for a N=1 trial database.
152002031	Real options to support decision making on reimbursement of expensive new inpatient drugs	Decision Making	To describe an alternative process for the adequate and timely decisions on reimbursement for expensive drugs,using the real options approach (ROA).	The research project has developed an instrument that allows setting the length of the period for evidence development by balancing costs and benefits of further evidence gathering. It uses information on prevalence, incidence, treatment duration and other relevant parameters.
152002032	Valuation of patient time	Costs & Outcomes	To develop and apply a method that can be used to value time of people that are undergoing treatment and especially focused on people not participating on the labor market.	The project resulted in a method that can be applied relatively straightforward to comprehensively value time of people not participating in the labour market and consuming expensive medicines.

Project Number	Title	Theme	Objective	Results
152002033	Measuring the effects of health interventions on subjective well-being comprehensively: The development and validation of the SWB-xD	Costs & Outcomes	Health interventions are likely to affect QoL in a broader sense than is measurable with existent health-related measures, such as the EQ-5D. In this proposal we identify the most relevant domains of well-being.	The most relevant domains of well-being are positive affect/happiness, physical independence, personal growth, autonomy and mental health
152002034	States worse than dead: measurement, estimation and interpretation	Design & Analysis	1) To assess the reliability of the Better than Dead method; 2) To develop and test statistical models to estimate time dependent values.; 3) to learn how respondents interpret the Better than Dead task.	A new method has been further developed, in which health states are compared with dead. Models were developed to assign values to the health states. These models can be used to quantify the health of patients and citizens. The method yields consistent scores for the EQ-5D health states. Maximal endurable time health states were successfully identified.
152002035	Optimal design and analysis for clinical trials in orphan diseases	Design & Analysis	To find the optimal trial design in orphan diseases by investigating efficiency and nuisance parameter sensitivity by comparing a classical fixed sample design and analysis against existing and new Bayesian approaches, as well as (group) sequential approaches in real and simulated data sets.	More insight in trial design for orphan diseases and pediatric research was generated. A systematic review of a number of publications on pediatric clinical trials shows misspecification of values necessary for sample size calculations, leading to an underestimation of the required sample size and subsequently, an insufficient answer of the research question. Several scenarios for pediatric clinical trials have been described. They aim to provide guidelines to clinical investigators for sample size calculations of phase III trials in children. Alternatives are proposed if the necessary numbers of children are not or less feasible, as in orphan diseases.
152002036	Marginal structural models for the analysis of time-dependent drug use in observational studies	Design & Analysis	To investigate whether an analysis with Marginal Structural Modelling can be applied to pharmaco-epidemiological research and to what extent this method has an added value for the analysis.	A MSM can be applied but the method does not always have an added value. The major problem is that time-dependent confounders are not always included in the observational study.
152002037	Web-based time trade-off incorporating interviewer help: Efficiency with validity	Costs & Outcomes	Obtaining TTO utilities is challenging and in most cases requires face-to-face interviews. The aim of this project is to develop an extended web-based TTO incorporating the help as from an interviewer.	The amount and nature of interviewer help in face-to-face interviews was examined. Overall 86% of participants need interviewer help at least once when rating health states on a TTO
152002038	When is it too expensive?	Decision Making	To examine the value of QALY gains, as relevant for the Dutch decision making model using a range of thresholds varying with severity of illness. This implies obtaining societal rather than individual valuations. A way of employing the willingness to pay (WTP) method to obtain relevant societal valuations of QALY gains will be developed. Its validity will be tested within the context of the study as well.	The results indicate that people do not give a higher value to QALYs gained in people with more severe diseases (like is the case in the current CVZ decision framework) but do vary the value strongly based on age of the recipient (which is not the case in the current CVZ framework). This finding was reflected in both the DCE and the WTP study. These results can be a reason to further investigate the current decision framework.
152002039	Test of lead time TTO in the general population	Costs & Outcomes	To explore possible refinements and improvements of the TTO method, in particular lead time TTO and lag time TTO for the valuation of poor health states. These alternative specifications of the TTO tasks offer a uniform procedure for the valuation of states better and worse than dead and therefore may resolve the problems.	A protocol for TTO studies was developed and an application for eliciting TTOs; a user support is offered in the form of training and a manual that describes the use of the application.

Project Number	Title	Theme	Objective	Results
152002040	Obtaining causal effect parameters from large databases using physicians preference as instrumental variable	Design & Analysis	To show the assumptions under which the instrumental variable analysis can be used to estimate reliably therapeutic effects in observational studies.	Preliminary results show that instrumental variable analyses estimate therapeutic effects considerably well. Results from these analyses are closer to effect estimates from standard analysis techniques based on the same data. However, effect estimates from instrumental variable analysis are captured with more uncertainty than standard analysis. This was established in simulation studies, and seem to depend on the size of the studied population.
152002041	Incorporating age-dependent reference points in health technology assessment	Decision Making	To develop a formal framework for integrating societal values on equity within a cost-utility analysis in a coherent and transparent way, while devoting special attention to the influence of reference levels concerning health. By making equity and reference-dependence more quantifiable, this approach is expected to improve the appraisal of health technology assessments.	This project has developed an assessment framework that allows both goals (efficiency and a fair distribution) to be considered and traded off against each other. Within this framework, an important element is the influence of what people perceive as a normal health state at different ages. People were found to perceive a highly deteriorated health state to be normal at older ages, which influences their preferences between different age groups and their degree of unfairness aversion by age group.
152002042	What is best when using drugs in chronic disease? A study that uses best-worst scaling to determine patient preferences for the process of drug use in Parkinson Disease	Costs & Outcomes	To develop a user-friendly, efficient and reliable method to assess the impact of drug use on the lives of people with a chronic disease, with a focus on measuring the impact of process of use. The study population for this study are people who are in the various stages of Parkinson's disease.	Preliminary results are on the influence of the treatment and disease on the health related quality of life of patients with Parkinson Disease. Non-motor symptoms mostly influence quality of life of patients. Most important positive results of treatment are on motor symptoms. Negative results were reported most frequently with regard to sleep and fatigue
152002043	Establishing reference prices from the national database of the DBC casemix system	Costs & Outcomes	To demonstrate the potential role of the diagnosis-treatment combination (DBC) database for use in economic evaluations, by developing costing methodologies to (a) determine treatment costs, (b) establish references prices and explore other research objectives, such as (c1) assessing the compliance to clinical practice guidelines, (c2) tracking treatment patterns over time and (c3) determining the costs of illnesses	Preliminary results indicate that future use of the national database for economic evaluations is constrained by the availability of data. When the identification of relevant patient subgroups depends on the (absent) clinical parameters (such as in breast cancer), no useful cost estimates can be made. When relevant subgroups can be identified (such as acute myocardial infarction), the use of the database results in valid cost estimates.
152002044	A Dutch tariff for the EQ-5D-5L	Costs & Outcomes	To establish Dutch social values for all 3125 health states of the EQ-5D-5L, to make this instrument suitable for use in pharmacoeconomic evaluations.	A tariff was developed which predicts values for the 3125 health states of the EQ-5D-5L.
152002045	HTA guidelines to assist in the decision making process for the reimbursement of orphan drugs	Decision Making	To develop guidelines for research on effectiveness, cost-effectiveness and budget impact of orphan drugs (drugs for rare diseases).	Preliminary results based on an exploration of foreign reimbursement decisions for the orphan drugs listed on the Dutch policy rule showed a negative correlation between the proportion of positive decisions and the cost of treatment (both per patient and overall budget impact). No relationship between the proportion of positive decisions and the rarity of the disease was observed.

Project Number	Title	Theme	Objective	Results
152002046	Integrating evidence on patient preferences in health care policy decisions: are we up for it?	Decision Making	To investigate whether, and if so, how and what type of evidence on patient preferences can be integrated in health care policy decisions regarding pharmaceuticals in The Netherlands, either in coverage decisions and/or in clinical practice guideline development.	Preliminary results: from interviews it became clear that the concept "preferences" is unclear and that there is no consensus on the integration of patient preferences in the reimbursement decision making nor in the development of clinical guidelines. Therefore, it will take more time and effort (to get feedback and gain consensus) before the decision framework can be developed.
152002047	Multiple imputation and bootstrapping in health economic data	Design & Analysis	To assess the bias of the invalid current methodology of a combined use of bootstrapping and multiple imputation, and to develop valid methodology that prevents underestimated uncertainty.	Preliminary results: to investigate neglected skewness 12 methods were developed and implemented to combine Multiple Imputation and Bootstrapping based on methods described in the literature. These methods were applied to simulated data sets and evaluated according to coverage and average length of the confidence intervals.
152002048	The risks of conditional reimbursement: stopping can be more difficult than not starting!	Decision Making	To study the risks of conditional reimbursement : (i) By studying under which conditions conditional reimbursement is considered feasible by decision makers and other stakeholders; (ii) By studying the gains versus losses discrepancy in this context in decision makers; (iii) By studying the same discrepancy in the general public	No results available yet
152002049	Are societal perspectives on resource allocation in health care reflected in recommendations and decisions about funding of costly end of life technologies?	Decision Making	To investigate which criteria the Dutch general public considers important for decisions about how to spend the health care budget optimally. Particular attention will be paid to the importance attached to expensive treatments at the end of life.	No results available yet
152002050	Disease models used for decisions on expensive drugs: a new instrument to enable structured model assessment.	Decision Making	To enhance the possibilities for decision makers and their advisors to transparently and consistently evaluate model based CEA results by developing a model assessment tool	Preliminary results: 1. Better insight into the definition and typology of model validation. 2. A gross list has been compiled with model validation techniques. These have been judged by an international panel on relevance and feasibility.
152002051	A roadmap for uncertainty analysis in MCDA	Decision Making	To develop a roadmap for identification, quantification and visualization of the role of uncertainty in use of MCDA in reimbursement decisions of medications and treatments	No results available yet
152002052	Taming uncertainty: Handling uncertainty in deciding upon new pharmaceuticals	Decision Making	To investigate how uncertainty can be better handled in policy decision making regarding pharmaceuticals	Preliminary results based on a literature search identified the following methods: foresight methods, scenario planning, exploratory meso models, data uncertainty engine, error propagation equations, expert elicitation, extended peer review, inverse modelling, Monte Carlo analysis, back casting, real options analysis, NUSAP (Numeral, Unit, Spread, Assessment, Pedigree) and sensitivity analysis.
152002053	Value judgment of (new) drugs in the Netherlands	Decision Making	To develop an instrument that can be used to support the existing decision making process for the Insured Package Advisory Committee (ACP) in their procedures for generating recommendations to the Minister of Health	No results available yet

Nederlandse organisatie
voor gezondheidsonderzoek
en zorginnovatie

Laan van Nieuw Oost-Indië 334
2593 CE Den Haag
Postbus 93245
2509 AE Den Haag
Telefoon 070 349 51 11
Fax 070 349 51 00
info@zonmw.nl
www.zonmw.nl

ZonMw