IMPROVING PATIENT ACCESS TO VALUABLE NEW PHARMACEUTICALS

Working towards an evidence ecosystem in healthcare

Rachel Rishma Johanna Kalf

Improving patient access to valuable new pharmaceuticals

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Colophon

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Het verbeteren van de toegang tot
waardevolle nieuwe geneesmiddelen
Werken aan een ecosysteem voor bewijs in de gezondheidszorg
(met een samenvatting in het Nederlands)

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Chapter 1

General introduction

Governments strive to ensure equal and timely access to new pharmaceuticals while keeping healthcare costs at an affordable level. Determining which pharmaceuticals add value to patients' lives requires a deep knowledge of the health outcomes that matter to patients and the use of instruments that adequately measure these outcomes. The development of a so-called evidence ecosystem[1] makes it possible to follow a new pharmaceutical through its lifecycle, including decisions about market authorization, reimbursement and healthcare delivery. To evaluate a pharmaceutical throughout its lifecycle it is important that health outcomes are as similar as possible between the processes within the evidence ecosystem. Additionally, there is a need for methods which allow for the coherent analysis of all available knowledge. This includes, but is not limited to, the analysis of different comparators used and the analysis of different types of evidence used (e.g. evidence from randomized controlled trials (RCTs) and real world evidence). The development of an evidence ecosystem allows for more efficiency within these processes, as duplication of work is limited, the same evidence is reusable in multiple settings, and ultimately pharmaceuticals which have a real value may reach patients earlier. This thesis focuses on the use of patient-relevant outcome data in health technology assessments (HTAs) underpinning reimbursement decisions, as well as on the potential to improve alignment between stakeholders in the healthcare field by assessing the overlap between HTA and market authorization on the one hand, and HTA and quality management of healthcare delivery on the other hand.

Affordable healthcare

Although healthcare budgets are limited, aging populations and the increasing number of patients with chronic diseases result in an increasing demand for healthcare. In addition, as health technologies lead to higher costs the sustainability of healthcare systems is threatened. HTA allows the identification of those health technologies which offer the best value for money and suggests how to allocate resources to achieve the greatest population health gains for the lowest possible cost. HTA is a multidisciplinary process which makes use of specific methods to determine the value of a health technology at different points in its lifecycle.[2] A health technology is an intervention which has been developed to prevent, diagnose or treat a medical condition, such as a medical device, a pharmaceutical, a surgical treatment or a vaccine.[2] The value of a health technology can be determined by assessing both the benefits and the costs of treatment. By weighing benefits against costs, HTA is used to inform healthcare decision-making, e.g. reimbursement decisions. HTA is a means

to achieve equal and timely access to new pharmaceuticals while containing healthcare costs.

Access to new pharmaceuticals

Before HTA agencies conduct their assessment for reimbursement recommendations, regulatory bodies, such as the European Medicine Agency (EMA) or the Food and Drug Administration (FDA) in the United States, assess new pharmaceuticals based on the risk and benefit balance in order to decide whether these pharmaceuticals should be authorized for market access. This assessment focusses on evaluating the safety, efficacy and quality.[3] In Europe, market authorization is conducted on European level by the EMA. Subsequently, reimbursement decision-making takes place. Reimbursement decision-making is an effort of national HTA agencies providing recommendations to national, regional or local decision-makers, such as Ministries of Health, national payers or local payers who make the final decision regarding reimbursement of new pharmaceuticals.[4] The recommendations provided by national HTA agencies for reimbursement decisions focuses on both the benefits and costs of treatment, which is based on a relative effectiveness assessment (REA), which may be combined with a cost-effectiveness assessment (CEA) and/or analysis of other aspects such as appropriate use of new pharmaceuticals.[5]

Although these processes are well established, countries may still struggle to provide timely and equal access to expensive innovative pharmaceuticals – even high-income countries.[6] Several reasons can be identified for this, two of which will be highlighted here. First, although regulatory and HTA decision-making are distinct processes and data needs may differ, both processes may be informed partly by similar data (i.e. clinical outcome measures and patient reported outcomes – PROs) preferably from RCTs. However, using comparable evidence regulatory bodies may authorize a pharmaceutical for market access, while HTA agencies may not recommend it for reimbursement.[7-9] Therefore, studies submitted by manufacturers that are suitable for regulatory decision-making may not be sufficient for HTA decision-making. Second, after manufacturers receive market authorization from regulatory bodies they may decide to refrain or delay the launch of a pharmaceutical commercially.[6] Low expected sales and insufficient profitability in a specific country may cause manufacturers not to submit a request for reimbursement recommendations from national HTA agencies.[6] This means that even though market access is granted new pharmaceuticals may still not become available to patients. This discord between

the process of market authorization and reimbursement recommendations possibly delays patient access to valuable new pharmaceuticals.

One solution to improve patient access to new pharmaceuticals is the increased collaboration between regulatory bodies and HTA agencies over the past years,[10, 11] for example joint or parallel scientific advice is more often conducted.[10-12] This has reduced the gap in evidentiary requirements between regulatory and HTA decision-making.[10-12] However, there may still be opportunity to further narrow this gap, such as increasing the agreement on for instance acceptable primary endpoints, using an appropriate comparator and using patient reported outcomes (PROs).[10,11,13,14] Some argue that choosing acceptable surrogate endpoints for both regulatory and HTA recommendations is important as well[9,10] although it is understandable that in the case of HTA – in which clinical benefits are balanced to costs – surrogate outcomes may always be insufficient. There is often a greater discord between regulatory bodies and HTA agencies when it comes to pharmaceuticals that come with high costs, significant impact on healthcare budgets, or a high degree of clinical uncertainty.[11] This is particularly notable for pharmaceuticals that receive conditional or accelerated approval and medicines for oncological or orphan diseases.[11] Clinical uncertainty may be due to the preliminary nature of some clinical data,[15] for example surrogate endpoints may be acceptable for regulatory decision-making but are not preferred for HTA decision-making. When differences in data requirements cannot be resolved, statistical methods may provide a potential solution.[12] However, such methods may add additional uncertainty in the evidence generated. Generating evidence which is relevant and acceptable for both regulatory bodies and HTA agencies will enable patient access to new innovative pharmaceuticals that provide value for money in a timely manner,[11,16] and promote an evidence ecosystem.

Since reimbursement recommendations are provided by national HTA agencies, differences in methods have been identified between HTA agencies in Europe leading to varying requirements for submissions.[11,12,14,17,18] Nevertheless, alignment exists between European HTA agencies in the evidence requirements necessary,[12] although some differences will remain. One important difference is the use of the most appropriate comparator which may differ between countries, since HTA agencies prefer to compare a new pharmaceutical to the standard of care used within that specific country.[12] In addition, clinical practice and standard of care change rapidly making it more difficult for manufacturers of pharmaceuticals to conduct RCTs including an appropriate comparator.[11]

To increase alignment between European HTA agencies and to stimulate collaboration and reduce duplication of work, the European Network for Health Technology Assessment (EUnetHTA) was established.[19] Recently, the European Union has created the Health Technology Assessment Regulation (HTAR) to further increase alignment between HTA agencies.[20] This regulation ensures the long-term sustainability of European HTA collaboration and allows a single EU-level submission for a joint REA of new pharmaceuticals. Non-clinical analysis, such as the budget impact or cost-effectiveness, and the final reimbursement recommendation remain the responsibility of national HTA agencies. In 2025 this regulation will apply for oncological pharmaceuticals and advanced therapy medicinal products (ATMPs). Subsequently, it will be extended to orphan drugs in 2028 and finally to all new pharmaceuticals from 2030 onwards.

Indirect treatment comparisons

Since the appropriate comparator preferred by national HTA agencies may differ between countries and the comparator necessary for regulatory decision-making may differ from the one necessary for HTA decision-making, head-to-head comparisons may not always be available. To allow analysis the use of indirect treatment comparisons (ITCs) may be considered.[10] ITCs make it possible to compare two treatments (e.g. A and B) to each other when head-to-head (direct) comparisons are unavailable. This may imply that for instance a third intervention (e.g. C) is used to which both treatments (e.g. A and B) were directly compared in a trial setting.[21] ITCs are widely accepted statistical methods and[22,23] have already been used for regulatory decision-making and HTA recommendations when the appropriate comparator was unavailable. However, including ITCs poses methodological difficulties and increases the uncertainty of clinical evidence.[12] Although the value of ITCs has been recognized,[12] current methods to conduct ITCs can still be improved.[24] In addition, differences exist in the acceptability of specific methods for ITCs between European HTA agencies.[25,26] However, the use of ITCs will become increasingly important as the HTAR comes into effect.

Importance of patient reported outcomes

For market authorization and reimbursement recommendations several outcomes are relevant. Traditionally regulatory bodies and HTA agencies focus on clinical outcome measures, such as mortality and morbidity. However, patient reported outcomes (PROs), such as health related quality of life (HRQoL), have become increasingly important.[27] New pharmaceuticals may sometimes offer limited added

benefits in terms of clinical outcome measures, but they could still substantially improve PROs. In clinical practice PROs are also increasingly important as clinicians involve patients more often in their treatment choices and use both clinical outcome measures and PROs to track how patients are doing.[28] Additionally, to improve the quality of healthcare several indicators, which may include PROs, are used by clinicians, regulators and payers.[29,30] Unfortunately, PROs are not yet systematically collected and are not always submitted by pharmaceutical manufacturers for regulatory or HTA assessment.[28]

PROs focus on the patient perspective, such as patients' perspective on the burden of adverse events or the influence of their treatment on their HRQoL, and are measured using patient reported outcome measures (PROMs), such as HRQoL questionnaires. Such insights are very difficult to retrieve through clinical outcome measures. Therefore, it is especially important to identify which aspects are relevant to patients. Several initiatives have assessed which clinical outcome measures and/or PRO(M)s are most relevant to patients. The International Consortium for Health Outcomes Measurement (ICHOM) has developed so-called standard sets that contain lists of standardized outcome measures, which they claim are most relevant to patients, for a specific condition.[31] These standard sets include both clinical outcome measures and PRO(M)s. Via the Core Outcome Measures in Effectiveness Trials (COMET) database other core outcome sets than the ICHOM standard sets, can be identified. Another initiative, the Patient-Reported Outcomes Measurement Information System (PROMIS), has developed self-report measures which can be used in the general population, and with adults and children with chronic condition(s). The literature on the patient relevance of PRO(M)s used in core outcome sets has not been consistent. Some authors suggest that PROMs used in ICHOM standard sets are relevant to patients,[32] whereas others question the relevance to patients.[33] This may be due to the fact that roughly 1 in 4 PROMs have been developed with no patient involvement.[34]

Patient involvement in the development of PROMs is deemed necessary to guarantee content validity. Content validity is the degree to which the content of an instrument adequately reflects the construct to be measured, e.g. health-related quality of life. Three aspects of content validity have been argued to be important: (1) the relevance of the items in a PROM, (2) the comprehensiveness of the PROM, and (3) the comprehensibility of the items for the intended patient group.[35] In order to ensure that all items are relevant and that no key items are missing, patients are often involved in PROM development through qualitative research methods such as focus groups, interviews, and concept mapping.[35] However, this type of

patient involvement can be time-consuming – both for patients and researchers – and is relatively expensive.[34] Alternatively, using existing patient stories could be considered in trying to capture the patient perspective, because many patients put their stories into writing and these stories offer insight into all aspects interrelated to life with a condition.[36] In this thesis, a specific source of patient stories will be explored, namely those published on social media.

Social media is a convenient and well-established source of data which is readily available. It provides a platform to patients to share their stories and experiences. Additionally, patients make use of social media to find information on their health condition and treatment options and to find social support.[37-40] A survey conducted by PatientsLikeMe showed that 11% of Americans use social media for reliable health information and 10% to find social support from their peers.[41] Social media has already been shown to help identify HRQoL topics of importance to patients, prioritize topics most relevant to patients, assess content validity of PROMs, and allow distribution of HRQoL questionnaires.[42-44] As such, social media may be a useful source of information regarding PROs for regulatory and HTA decision-making, as well as inform quality of healthcare.

Quality management of healthcare

Since the main purpose of HTA is evidence-based selection of health technologies and their appropriate use in healthcare,[45] it indirectly contributes to improving the quality of healthcare.[14] Healthcare quality can be defined as 'the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge'.[46] Dimensions regarding effectiveness, safety, patient-centeredness, timeliness, efficiency and equity are included herein, which highlights the conceptual overlap with HTA. In addition, some national HTA agencies also support the development of standards, guidelines and other healthcare policies to improve the quality of healthcare.[14,47] For example, the Dutch National Health Care Institute (ZIN) supports the collaboration between healthcare professionals, patients and insurers in the development of quality standards. Healthcare providers are obligated to report these, and this information is published by ZIN on a public database.[48,49] The English National Institute for Health and Care Excellence (NICE) collaborates with stakeholders in the development of quality standards, and publishes these on their website. However, these quality standards are not mandatory.[50] In addition, there is a growing interest to align activities on HTA and healthcare quality. Therefore, some HTA agencies have increased their collaboration with clinicians especially regarding the development of clinical guidelines. A clear example is that currently several HTA agencies have become a member of the Guidelines International Network (GIN),

which is a network of organisations and individuals with the ambition to improve the quality of healthcare by promoting evidence-based guideline development, adaptation, dissemination and implementation.[51]

Although HTA and the improvement of healthcare quality may be perceived as distinct processes, they depend on each other and are in some cases closely linked.[52] While HTA focuses on the systematic evaluation of health technologies to inform reimbursement decision-making and quality improvement on the proper use of the best available knowledge in healthcare in order to improve health outcomes,[53,54] there is a growing believe that increasing alignment of these processes may contribute to an evidence ecosystem. Within this evidence ecosystem it would be possible to follow a new pharmaceutical through its lifecycle. After a pharmaceutical receives a positive reimbursement recommendation and subsequently enters clinical practice the impact on clinical outcome measures and PROs found in the RCTs submitted by manufacturers to gain reimbursement may be corroborated with real world evidence found in clinical practice. To do so, some alignment in the clinical outcome measures and PRO(M)s used for HTA recommendations and healthcare quality improvement is important. Standardizing outcome measures might also limit the number of PROMs patients need to complete and limit the disruption of clinicians workflow. In addition, alignment between HTA and quality of healthcare is important to ensure that delivered healthcare matches the care being reimbursed.

Thesis objective

The overall aim of this thesis is to assess how HTA decision-making can become more patient-relevant and aligned with other stakeholders in the healthcare field. The following research questions are therefore explored in this thesis:

- How patient-relevant are the outcome measures used in regulatory decision-making, HTA recommendations and healthcare quality improvement?
- How can alignment between outcome measures used for regulatory and HTA recommendations, and HTA recommendations and healthcare quality improvement be improved?
- What are the possibilities of using social media for obtaining information that is relevant for HTA recommendations?
- Which methods and practices are currently used regarding ITCs employed in HTA recommendations?

Outline of this thesis

Part A describes the overlap between the outcome measures used in regulatory decision-making, HTA decision-making, quality improvement and how this relates to those outcome measures that matter most to patients by using ICHOM standard sets. **Chapter 2** focuses on the overlap between regulatory and HTA guidelines and how these compare to ICHOM standard sets, while **Chapter 3** discusses the extent to which outcome measures used in HTA reports and those used in healthcare quality improvement compare to ICHOM standard sets.

Part B focuses on social media and how this type of information could contribute to HTA recommendations. **Chapter 4** shows which type of information could be collected via social media and whether there are benefits for HTA. In **Chapter 5** social media was used to distribute a survey to melanoma patients in order to assess which HRQoL aspects are perceived to be most relevant. **Chapter 6** provides insight into the use of online forums to listen to melanoma patients and to observe which topics are discussed relating to HRQoL.

Part C discusses the potential of using ITCs for HTA. **Chapter 7** specifically focuses on how often ITCs are used, which methods are employed and what the influence of ITCs are on reimbursement recommendations in HTA conducted in the Netherlands and England.

Finally, **Chapter 8** provides a general discussion, in which the results of all studies are summarized and put into a broader perspective with recommendations for future research.

Authorship Statement

RK wrote the introduction, while her supervisory team provided feedback during the whole process. RK implemented this feedback and her supervisory team approved the final version.

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Part A

Patient relevance of outcome measures used in regulatory decision-making, health technology assessment recommendations and quality of healthcare

Chapter 2

Bridging the gap: Can International Consortium of Health Outcomes Measurement standard sets align outcomes accepted for regulatory and health technology assessment decision-making of oncology medicines

Rachel R.J. Kalf, Rick A. Vreman, Diana M.J. Delnoij, Marcel L. Bouvy, Wim G. Goettsch

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Abstract

Standard outcome sets developed by the International Consortium for Health Outcomes Measurement (ICHOM) facilitate value based healthcare in healthcare practice, and have gained traction from regulators and Health Technology Assessment (HTA) agencies that regularly assess the value of new medicines. We aim to assess the extent to which the outcomes used by regulators and HTA agencies are patient relevant, by comparing these to ICHOM standard sets. We conducted a cross-sectional comparative analysis of ICHOM standard sets, and publicly available regulatory and HTA assessment guidelines. We focused on oncology due to many new medicines being developed which are accompanied by substantial uncertainty regarding the relevance of these treatments for patients. A comparison of regulatory and HTA assessment guidelines, and ICHOM standard sets showed that both ICHOM and regulators stress the importance of disease-specific outcomes. On the other hand, HTA agencies have a stronger focus on generic outcomes in order to allow comparisons across disease areas. Overall similar outcomes are relevant for market access, reimbursement and in ICHOM standard sets. However, some differences are apparent, such as the acceptability of intermediate outcomes. These are recommended in ICHOM standard sets, but regulators are more likely to accept intermediate outcomes than HTA agencies. A greater level of alignment in outcomes accepted may enhance the efficiency of regulatory and HTA processes, and increase timely access to new medicines. ICHOM standard sets may help align these outcomes. However, some differences in outcomes used may remain due to the different purposes of regulatory and HTA decision-making.

Introduction

Value of healthcare is becoming more important than only assessing the volume provided, since healthcare costs are rising faster than available healthcare budgets.[1] One of the concepts that tries to address this is value based healthcare (VBHC), which aims to achieve the best possible health outcomes to patients for the lowest possible cost.[1,2] A vital element of VBHC is the collection of health outcomes through a standardized approach.[1] The International Consortium for Health Outcomes Measurement (ICHOM) has developed so-called standard sets, that focus on outcomes that are relevant for patients and that may facilitate the evaluation of VBHC in healthcare practice.[3]

VBHC has been embraced in the assessment of innovative medicines, since it focusses on improving the value for money in healthcare and may support regulatory and HTA processes.[4] Regulatory bodies authorize innovative medicines for market access based on the scientific assessment of the efficacy, safety and pharmaceutical quality. Subsequently, Health Technology Assessment (HTA) agencies conduct an assessment of these innovative medicines for pricing and reimbursement decisions which focus on a relative effectiveness and/or cost-utility analysis.[5] Regulatory bodies and HTA agencies mostly use similar clinical data for their assessments, preferably from randomised clinical trials.

The use of outcomes relevant to patients is important in VBHC, as well as in regulatory and HTA assessments. However, based on an application containing similar evidence regulatory bodies may authorize an innovative medicine for market access, while HTA agencies may not approve it for reimbursement.[6-10] Although different perspectives to the relevance of outcomes may be due to the different remits of regulatory bodies and HTA agencies, some alignment in the use of those outcomes may promote more consistent and timely access to valuable innovative medicines.[10-13] Since ICHOM claims to include health outcomes that matter most to patients and has involved patient representatives to develop standard sets,[14-16] it may be an initiative which could support this further alignment. Therefore, we aim to assess the extent to which the outcomes used by regulatory bodies and HTA agencies are patient relevant by comparing these outcomes to those defined by ICHOM.

Methods

We conducted a cross-sectional comparative analysis of the content of ICHOM standard sets, and publicly available regulatory and HTA assessment guidelines. These assessment guidelines provide instructions to pharmaceutical companies who intend to submit an application for the assessment of an innovative drug regarding marketing authorization or pricing and reimbursement decision-making. We especially focused on oncological indications, because currently many new oncology medicines are developed which are accompanied with substantial uncertainty on the relevance of these treatments for patients. Additionally, different ICHOM standard sets are available for several types of cancer. We extracted regulatory assessment guidelines with a focus on oncology and additionally identified general HTA assessment guidelines.

In particular, we identified in November 2018 five ICHOM standard sets that focus on oncological conditions.[3] These standard sets included colorectal cancer,[17] breast cancer,[18] lung cancer,[19] localized prostate cancer [20] and advanced prostate cancer.[21] ICHOM is a not-for-profit organisation which aims to develop a minimum set of standardized outcomes which really matter to patients.[3] Each standard set provides a recommendation on the outcomes, including patient reported outcome measures (PROMs), that are relevant to patients with a specific medical condition. ICHOM standard sets are developed over a period of nine months in International Working Groups that consist of 15 to 20 members, and include leading clinicians, outcomes researchers, registry leaders and patient advocates. The outcomes that are included in the standard sets are selected based on several criteria, such as psychometric quality and burden of assessment.[3] Before completing a standard set key stakeholders are invited for an open review.

For the assessment of the regulatory guidelines, two regulatory bodies were included, which represent the two regions (the United States and Europe) with the highest spending on pharmaceuticals worldwide,[22,23] namely: the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). For the HTA guidelines we selected three HTA agenies representing three European jurisdictions for inclusion: the Dutch National Health Care Institute (ZIN), the National Institute for Health and Care Excellence (NICE) and the Institute for Quality and Efficiency in Health Care (IQWiG). NICE and IQWiG represent two of the four largest European jurisdictions, and ZIN and NICE are recognized as pioneers within HTA by actively collaborating within different European projects. One platform that

facilitates the collaboration between European HTA agencies to conduct relative effectiveness assessments on a European level was also included: the European Network for Health Technology Assessment (EUnetHTA).[24] EUnetHTA is funded by the European Union to facilitate HTA collaboration in Europe. HTA agencies and institutes from 30 European countries have become involved as partners. In order to support efficient production and use of HTA in European countries, EUnetHTA facilitates joint assessments. These assessments are produced by at least four EUnetHTA partners in different European countries, and can be used for HTA decision-making by all EUnetHTA partners. In addition, EUnetHTA developed the 'HTA core model' which is a methodological framework for the production and sharing of HTA information.

To identify regulatory and HTA assessment guidelines, author RK first searched the websites of the regulatory bodies and HTA agencies between mid-October and mid-November 2018. During this search weblinks on the homepage were used, as well as the following search terms: endpoint, outcome measure, oncology, cancer, assessment, colon cancer, lung cancer, prostate cancer, breast cancer, patient reported outcome, and endpoint oncology. Second, assessment guidelines were included if they were published in English or Dutch, were final documents, focused on market authorisation or pricing and reimbursement decision-making, and focused on the acceptability of outcomes.

In order to extract data from the ICHOM standard sets, and regulatory and HTA assessment guidelines we developed a standardized coding scheme by deductive content analysis.[25] Authors RK and RV independently assigned codes to the ICHOM standard set about colorectal cancer, the EMA guideline 'Guideline on the evaluation of anticancer medicinal products in man', and the NICE guideline 'Guide to the methods of technology appraisal 2013'. Any disagreements were discussed and resolved by consensus. Based on these discussions the standardized coding scheme was assessed and adjusted where needed. Subsequently, authors RK and RV independently assessed the ICHOM standard set about breast cancer, the FDA guideline 'Guidance for industry clinical trial endpoints for the approval of cancer drugs and biologics' and the IQWiG guideline 'General methods version 5.0'. The remaining standard sets and assessment guidelines were coded by author RK, since a second reviewer was deemed unnecessary based on the degree of consensus after two rounds of validation on 6 documents in total. All data were stored and analysed using NVIVO 12.[26]

Results

Based on the website search five ICHOM standard sets and 50 assessment guidelines were identified (Figure 1). All five ICHOM standard sets were included. Of the 50 assessment guidelines identified a total of 15 were excluded due to the lack of focus on discussing the acceptability of outcomes in assessments, 5 were excluded because these were draft documents, 5 were excluded because they were duplicates, and 3 were excluded due to lacking focus on market access or reimbursement assessments. In total 22 assessment guidelines were included since these focussed on providing guidance on the acceptability of outcomes, of these ten were published by a regulatory body and twelve were published by an HTA agency or EUnetHTA. Both regulatory bodies published general assessment guidelines for oncological products, in addition both provided guidelines for specific oncological conditions including breast cancer (FDA and EMA), lung cancer (FDA and EMA), and prostate cancer (EMA). All HTA agencies and EUnetHTA published assessment guidelines for medical conditions in general. Separate information was provided in these guidelines regarding relative effectiveness assessments and cost-effectiveness assessments. In addition, IQWiG published a guideline focusing on the use of intermediate outcomes in oncology.

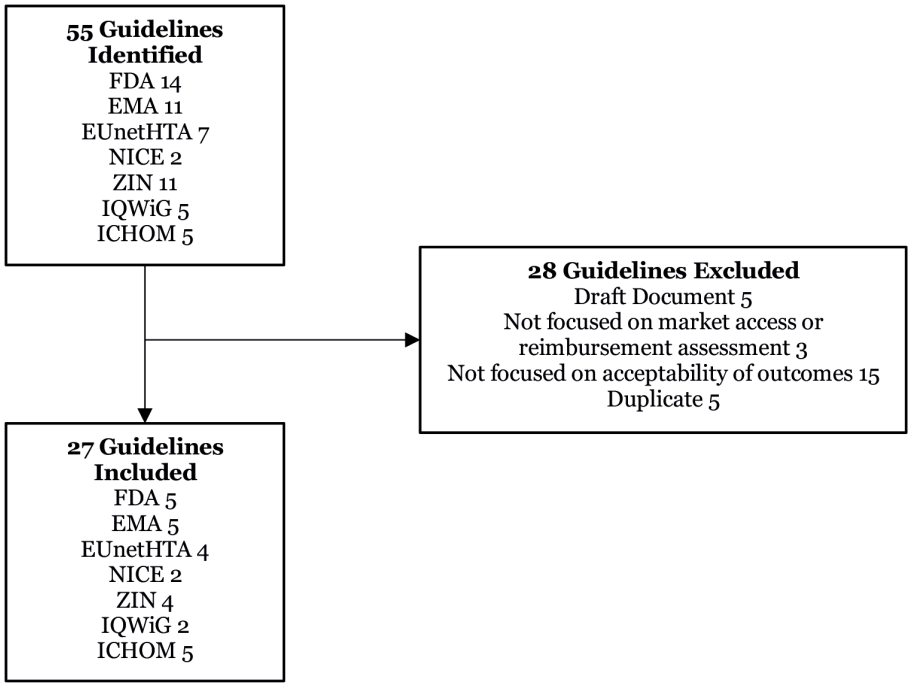

Figure 1. Flowchart of guideline identification, and in- and exclusion

Mortality estimates were mentioned in all the guidelines and standard sets. The specific term 'mortality' was used by EUnetHTA, NICE, IQWiG and ZIN, other terms used include 'survival' (ZIN, EUnetHTA, NICE, FDA), 'overall survival' (EUnetHTA, NICE, FDA, EMA, ICHOM) and 'increase in life expectancy' (ZIN, IQWiG; Table 1 and Appendix 1). EUnetHTA, FDA and EMA accepted overall survival (OS) as the most persuasive outcome to estimate clinical benefit (data not shown), likewise ICHOM recommended OS as an outcome in all included standard sets (Table 2). Definitive outcomes, such as survival, were accepted by NICE, ZIN, IQWiG, FDA and EMA as primary outcomes in their assessments (Table 3 and Appendix 2).

Table 1. Acceptability of outcomes in regulatory and HTA decision-making of innovative medicines as compared to ICHOM standard sets

Outcomes	**HTA**		**Regulatory**	**ICHOM**
	Reimbursement		**Market Approval**	**Value Based Healthcare**
	REA	**CEA**		
Mortality	X	X	X	X
Morbidity	X	X	X	X
Safety	X	X	X	X
Intermediate outcomes				
Progression	X	X	X†	X
PFS	X	X	X†	X
DFS	X	-	X†	-
EFS	-	X	X	-
TTP	-	-	X†	-
RFS	-	-	-	X
Tumour Response	-	-	X†	X
PROMs	X	X	X	X
Symptom Reduction	X	-	X	X
HRQoL	X	X	X	X
QALY	-	X	-	-
Composite outcomes	X	X	X	-
Biomarkers	X	-	X	-

† The FDA allows this outcome to be included in the assessment for accelerated approval and regular approval.

Abbreviations: X this outcome was mentioned in the guideline or standard set; - this outcome was not discussed or mentioned in the guideline or standard set; HTA Health Technology Assessment; ICHOM International Consortium for Health Outcomes Measurement; REA Relative Effectiveness Assessment; CEA Cost-Effectiveness Assessment; PFS Progression Free Survival; DFS Disease Free Survival; EFS Event Free Survival; TTP Time To Progression; RFS Regression Free Survival; PROMs Patient Reported Outcome Measures; HRQoL Health Related Quality of Life; QALY Quality Adjusted Life Year.

Collection of morbidity estimates as well as safety estimates (e.g. adverse events, complications) was discussed by all HTA agencies, regulatory bodies and in all ICHOM standard sets (Table 1 and Appendix 1).

Intermediate outcomes were accepted, sometimes under certain conditions, by all regulatory bodies, ICHOM standard sets, and HTA agencies (Table 1, Table 3 and Appendix 2). For example, the FDA specified 'surrogate endpoints for accelerated approval must be reasonably likely to predict clinical benefit', which suggests validity does not always have to be fully established. All HTA agencies mentioned the importance of including valid intermediate outcomes, meaning an established relationship between the intermediate (e.g. progression free survival) and definitive outcome (e.g. survival). However, the level of validity which was acceptable differs between HTA agencies (e.g. IQWiG required a higher level of validity than ZIN, NICE or EUnetHTA). IQWiG published a guideline regarding the use of intermediate outcomes in oncology, which highlighted the importance of assessing the validity of an intermediate outcome. More specifically, based on validation studies for colon and breast cancer regarding the use of intermediate outcomes for survival, IQWiG found the validity insufficient to allow any final conclusions based on these intermediate outcomes.[27]

Disease progression estimates were accepted by all HTA agencies, except for IQWiG, both regulatory bodies and in ICHOM standard sets (Table 1 and Appendix 1). In disease specific guidelines for lung, breast and prostate cancer progression estimates were acceptable for both the FDA and EMA, whereas ICHOM suggested the collection of progression estimates for breast cancer and colorectal cancer (Table 2 and Appendix 1).

Table 2. Acceptability of outcomes specific for lung cancer, breast cancer and prostate cancer as published by FDA and EMA, in addition to their general guidelines, and ICHOM

Outcome	**FDA**	**EMA**	**ICHOM**
	Market Approval	**Market Approval**	**Value Based Healthcare**
Lung Cancer			
Overall Survival	X	X	X
Progression			
PFS	X†	X	-
DFS	X	-	-
TTP	X†	-	-
Tumour Response	X†	X‡	

Table 2. Continued

Outcome	FDA	EMA	ICHOM
	Market Approval	**Market Approval**	**Value Based Healthcare**
PROMs	X	X	X
HRQoL	-	X	X
Reduction Symptoms	X	-	-
Safety	-	-	X
Breast Cancer			
Overall Survival	X	X	X
Progression			
PFS	-	X	-
DFS	X	X	-
EFS	X	X	-
RFS	-	-	X
Tumour response	X†	X	-
PROMs	-	-	X
HRQoL	-	-	X
Safety	-	X	X
Prostate Cancer			
Overall Survival	N/A	X	X
Progression			X§
PFS		X	-
DFS		X	-
Distant metastases-free survival		X	-
PROMs	N/A	X	X
HRQoL		-	X
Safety	N/A	-	X
Other		-	X
Use of pain medication		-	X
Symptomatic skeletal event			

† FDA may use PFS, TTP and tumour response rates for lung cancer to support both regular and accelerated approval, and specifically allows tumour response rates for breast cancer to support accelerated approval

‡ EMA may accept tumour response rates as outcome in exploratory studies for early evaluation approvals

§ ICHOM recommends the collection of the following outcomes for prostate cancer regarding progression: development of metastasis (advanced and localized prostate cancer), development of castration-resistant disease (advanced prostate cancer), biochemical recurrence (localized prostate cancer), procedures needed for local progression (advanced prostate cancer).

Abbreviations: FDA Food and Drug Administration; EMA European Medicines Agency; ICHOM International Consortium for Health Outcomes Measurement; PFS Progression Free Survival; DFS Disease Free Survival; TTP Time To Progression; PROMs Patient Reported Outcome Measures; HRQoL Health Related Quality of Life; EFS Event Free Survival; RFS Regression Free Survival; N/A Not Applicable.

PROMs were discussed in all guidelines and standard sets (Table 1 and Appendix 1). The reduction of symptoms was an acceptable outcome for EUnetHTA, IQWiG, FDA and EMA. In the ICHOM standard sets the reduction of symptoms was included in disease specific HRQoL questionnaires, such as questions regarding arm and breast symptoms in the case of breast cancer (data not shown). The term 'health related quality of life' was mentioned in all the guidelines and standard sets. All HTA agencies recommended the use of a generic HRQoL instrument, both NICE and ZIN specifically recommended the use of the EQ-5D. In addition to a generic HRQoL instrument, EUnetHTA, ZIN and IQWiG mentioned the acceptability of disease specific HRQoL instruments to complement generic instruments. The EUnetHTA guideline specified 'Disease-specific HRQoL instruments may be useful for more in-depth assessment of the generic HRQoL dimensions affected by an intervention'.[28] Both regulatory bodies indicated that the use of a validated or a generally accepted HRQoL instrument was important, additionally, the EMA specifically mentioned that a HRQoL questionnaire may be generic or disease specific. In all ICHOM standard sets disease specific HRQoL instruments were recommended, such as the EORTC QLQ-C30 and EORTC QLQ-LC13 for lung cancer, and EORTC-QLQ-C30 and EORTC-QLQ-CR29 for colorectal cancer (Table 2 and Appendix 1).

The term 'biomarker' was mentioned in the guidelines of EUnetHTA, NICE, IQWiG, FDA and EMA (Table 1 and Appendix 1). NICE and IQWiG specifically indicated biomarkers may be used to support treatment decisions, therefore, biomarkers seem to be mainly used to identify specific patient groups to target for treatment. However, the FDA mentioned in their guidelines that biomarkers have not served as primary outcomes for cancer drug approval, however 'the FDA has accepted tumour markers as elements of a composite endpoint'.[29]

Estimates for tumour response (e.g. partial complete response, objective response rate) were accepted by both regulatory bodies and ICHOM (Table 1 and Appendix 1). Tumour response was mentioned as acceptable outcome in the FDA and EMA guidelines for lung cancer and breast cancer, while ICHOM recommended tumour response for colorectal cancer (Appendix 1). The acceptability of tumour response as outcome in prostate cancer was not mentioned by the EMA or for breast cancer, lung cancer or (localized or advanced) prostate cancer by ICHOM (Table 2 and Appendix 1).

Finally, ICHOM suggested some outcomes which were not mentioned by the regulatory bodies or HTA agencies, including place of death, stoma status, and reoperation due to positive margins (Table 3).

Table 3. Hierarchy of outcomes accepted by regulatory bodies, HTA agencies, and ICHOM

Institute	Primary outcomes	Secondary outcomes
EUnetHTA		Non-definitive outcomes (e.g. morbidity, function, HRQoL), ADRs
Life-threatening disease	Long-term and definitive outcomes (e.g. mortality or survival), ADRs, PFS[d], HRQoL[g]	Morbidity, HRQoL
Non-life threatening disease	Mortality or survival	Not mentioned
First assessment	Morbidity, PROMs, HRQoL	Not mentioned
Re-assessment	Definitive clinical outcomes (e.g. mortality and survival)	Not mentioned
Economic evaluation	Definitive clinical outcomes on morbidity and mortality (e.g. stroke, fracture) Life years gained, QALYs	Not mentioned
FDA	Survival improvement, OS, PROMs, intermediate outcomes, PFS, improvement in physical functioning or tumour-related symptoms, time to progression of cancer symptoms, toxicity, improvement in DFS[d], durable complete response[d], substantiated ORR[d], TTP[f]	Tumour measurement and response, PROMs,
Regular approval	Intermediate outcomes, DFS, PFS, TTP, ORR, CR	HRQoL, biomarkers
Accelerated approval		Not mentioned
EMA	Efficacy (e.g. survival), safety (e.g. tolerability and severe or life-threatening ADRs), TTP[d], PFS[d], time to symptomatic tumour progression[d]	HRQoL, symptom deterioration, PROMs
Single agents & combination therapies	Cure rate, OS, PFS, DFS, event rate[d], symptom control[d], time to symptomatic progression[d]	ORR, rate of tumour stability, symptomatic tumour progression, HRQoL, PROMs
Treatment with curative intent	PFS[b,d] ,DFS[e], EFS[b], ORR[b], increased cure rate[c], OS[c], EFS[d], CR[a,d], CR+PR[a,d], major increase ORR[b,d], major increase in EFS[c,d] or PFS[c,d]	Not mentioned
Treatment intended to achieve long term disease control	PFS[a,b], improved survival[c], major benefit in PFS[c,d]	Not mentioned
Palliative therapy	Prolonged OS, improved symptomatic control, HRQoL	Not mentioned

Table 3. Continued

Institute	Primary outcomes	Secondary outcomes
Adjuvant therapy	Increased cure rate, OS, DFS[d], safety[d]	CR
Neo-adjuvant therapy	OS, PFS, DFS, enabling surgery and organ preservation	Not mentioned
ICHOM	OS, PROMs, complications[i], cause specific survival[j], cause of death[j], treatment related mortality[j], place of death[i,j], preference for place of death[i,j], RFS[i,j], PFS[i,j], PCR[i,j], CR[i,j], margin status[i,j], biochemical recurrence[j], reoperation due to positive margins[j], procedures for local progression[j], symptomatic skeletal event[j], development of metastasis[j], development of castration-resistant disease[j], stoma status[j], use of pain medicine[j], time from diagnosis to treatment[j], hospital admission at the end of life[i,j]	Not mentioned

[a] When reduced or similar toxicity is expected

[b] When increased toxicity is expected

[c] When a major increase in toxicity is expected

[d] By exception this outcome may be used as primary outcome. This may be related to a specific patient population or treatment, for example for patients with solid tumours, in small populations, in the adjuvant setting, or in late line therapy

[e] When improved cure rate is the objective

[f] When the majority of deaths is unrelated to cancer

[g] HRQoL may be used as a primary outcome when the questionnaire was developed with the objective to capture the specific impact of a given pathology

[h] This outcome may by exception be used as primary outcome

[i] ICHOM recommends to assess these for a specific group of patients, e.g. patients with advanced disease or patients with curative intent.

[j] ICHOM recommends this outcome for a selection of indications: reoperation due to positive margins for breast cancer; time from diagnosis to treatment, treatment related mortality for lung cancer; stoma status, PFS, PCR or CR, margin status, preference for place of death, hospital admission at the end of life for colorectal cancer; use of pain medicine, procedures for local progression, symptomatic skeletal event, development of metastasis, development of castration-resistant disease for advanced prostate cancer; biochemical recurrence and development of metastasis for localized prostate cancer; cause specific survival for advanced and localized prostate cancer; RFS for breast cancer and colorectal cancer; place of death for colorectal cancer and lung cancer; cause of death for breast cancer, colorectal cancer and lung cancer

Abbreviations: HTA Health Technology Assessment; EUnetHTA European network for Health Technology Assessment; NICE the National Institute for Health and Care Excellence; ZIN the Dutch National Health Care Institute; IQWiG the Institute for Quality and Efficiency in Health Care; FDA Food and Drug Administration; EMA European Medicines Agency; PROMs Patient Reported Outcome Measures; HRQoL Health Related Quality of Life; QALY Quality Adjusted Life Year; PFS Progression Free Survival; ADRs Adverse Drug Reactions; OS Overall Survival; DFS Disease Free Survival; TTP Time To Progression; ORR Objective Response Rate; CR Complete Response; EFS Event Free Survival; PR Partial Response;

Discussion

This study confirms that outcomes that matter to patients are mostly also relevant for market access and reimbursement. However, some differences remain, which is especially apparent regarding the acceptability of intermediate outcomes. These are recommended in ICHOM standard sets, but regulatory bodies are more likely to accept these than HTA agencies. ICHOM standard sets emphasize the importance of collecting all recommended outcomes, while regulatory and HTA guidelines only indicate that all relevant outcomes should be collected. When considering disease specific guidelines, both regulatory bodies and ICHOM standard sets recommend collection of OS. However, differences appear regarding the collection of other outcomes. For example, tumour response is accepted by both regulatory bodies for lung and breast cancer, while ICHOM only recommends this outcome for colorectal cancer.

We showed that OS is viewed by the EMA and FDA as the most persuasive evidence, which confirms previous findings.[30] In HTA assessments regarding the relative effectiveness of oncological medicines it has been shown that data on OS are most crucial for decision-making on the value of these products.[8] However, OS data is not always mature when submitted for regulatory or HTA assessment.[8,30,31] Therefore, intermediate outcomes, such as progression free survival, may be accepted by regulatory bodies[30,31] and HTA agencies.[4,5] However, our study suggests that regulatory bodies are often less stringent regarding the acceptability of intermediate outcomes than HTA agencies, which is confirmed by previous studies.[32,33] The FDA, for example, accepts intermediate outcomes that will reasonably likely predict clinical benefit for accelerated approval, whereas HTA agencies only accept validated intermediate outcomes. Additionally, between HTA agencies the required level of validity also varies, which was also demonstrated in the study of Kleijnen et al.[8]

By comparing outcomes accepted by regulatory bodies and HTA agencies to ICHOM standard sets we have added another dimension to this discussion. This study showed a difference in the use of generic and disease specific guidelines, where HTA agencies provide generic guidelines, regulatory bodies oncology specific guidelines, and ICHOM disease specific guidance. Although HTA agencies generally require generic outcomes to allow comparability between indications for their reimbursement decision-making, additional disease-specific outcomes could help to identify to which extent new oncological medicines will affect the quality of life of patients. ICHOM could assist HTA

agencies in choosing outcomes most relevant to patients. Additionally, when both regulatory bodies and HTA agencies make use of ICHOM standard sets to define acceptable outcomes these may become better aligned.

To improve the timely access of new medicines that provide a real benefit to patients, and enhance the efficiency of regulatory and HTA processes alignment between these processes is becoming increasingly important.[6,7,11,12] Synergy may be created by sharing information, choosing similar outcomes, aligning the timing of procedures, parallel scientific advice, and collaboration around real world evidence generation.[6,8-11,13,32,34] Although regulatory and HTA processes have different purposes, which partly may explain their different perspectives on outcomes and subsequent conclusions, increasing alignment is important to support more equal access to medicines for European patients and may also be feasible as previous studies have outlined several options to increase alignment.[9,33,35-37] A possible further alignment of the regulatory and HTA processes needs further collaboration and additional discussion between all stakeholders involved.[10]

HRQoL is a PROM where more alignment between regulatory and HTA assessments may be possible.[9] Regulatory bodies accept both disease specific and generic HRQoL questionnaires, while HTA agencies mostly rely on generic HRQoL questionnaires because it also needs to fulfil the requirements for their economic evaluations. On the other hand, ICHOM standard sets indicate the importance of using disease specific HRQoL questionnaires. Methods, such as mapping, may be used to extrapolate results from disease specific questionnaires to calculate generic quality of life which could be used in HTA economic evaluations. However, HTA agencies are generally not prone to use this specific method, because of the possible biases involved. Nevertheless, other methods may be explored which could be acceptable for HTA agencies to use.

This study has some limitations. First, we selected regulatory bodies and HTA agencies situated in Europe, except for the FDA which is based in the United States. Therefore, we do not provide a global perspective on regulatory and HTA assessment guidelines. Second, we assessed regulatory and HTA assessment guidelines and not the actual assessment reports. We decided to first assess which outcomes would be preferred before looking into the difference between the ideal and actual situation. However, in practice it may not always be feasible to collect these outcomes. Therefore, regulatory bodies and HTA agencies may accept different outcomes than discussed in assessment guidelines.

A strength of this study is the inclusion of ICHOM standard sets to assess outcomes which are believed to be relevant to patients. Some publications suggest that ICHOM standard sets use PROMS that are satisfying to patients.[14] However, the extent to which these standard sets are patient relevant may also be questioned.[38] Some of the PROMS recommended by ICHOM standard sets seem to have been developed with limited patient involvement. For example, the HOOS-Physical Function Short Form was included by the ICHOM standard set for Hip and Knee Osteoarthritis, while a study showed that some questions were unimportant to Dutch patients.[38]

To increase early access to medicines with an added value a greater level of alignment is of importance to all stakeholders involved. Further collaboration and additional discussions are needed between these stakeholders to progress further possible alignment between regulatory bodies, HTA agencies, patients and clinicians on the most relevant outcomes for decision-making. However, we still need to realise that regulatory and HTA processes have different contexts and distinct purposes, where regulatory bodies determine whether a medicine is effective and has acceptable side effects while HTA agencies assess the effectiveness of a medicine to what is used in clinical practice and whether its added value is reasonable compared to the additional costs. This may necessitate some differences in the outcomes used. Additionally, some outcomes are more likely to be accepted by regulators than HTA agencies, therefore medicines that gain market access may not become available to patients due to a negative reimbursement decision. To ensure pharmaceutical companies are aware of the outcomes necessary for market access and reimbursement assessments conducting early parallel scientific advice with regulatory bodies and HTA agencies is relevant. To conclude, it is envisioned that in future concepts of VBHC in which market authorization, reimbursement decision-making and quality control of healthcare come more closely together, the use of outcomes will be much more aligned.

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Authorship Statement

RK designed the study in collaboration with the co-authors. RK collected the data together with author RV. RK subsequently analysed the data, and wrote the draft manuscript. All co-authors actively contributed throughout the conduct of the study and critically reviewed and approved the manuscript.

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Appendices

Appendix 1. Acceptability of outcomes in the approval for market authorization by regulatory bodies, and in the use of cost-effectiveness and relative effectiveness assessment of HTA agencies as compared to ICHOM standard sets for each organisation separately

Outcome	EUnetHTA		NICE		ZIN	
	Reimbursement		Reimbursement		Reimbursement	
	REA	CEA	REA	CEA	REA	CEA
Mortality	X	X	X	X	X	X
Morbidity	X	-	-	-	X	X
Safety	X	-	X	-	X	X
Intermediate outcomes						
Progression	X	X	X	X	X	X
PFS	X	-	X	X	-	-
DFS	X	-	-	-	-	-
EFS	-	-	-	-	-	X
TTP	-	-	-	-	-	-
RFS	-	-	-	-	-	-
Tumour response	-	-	-	-	-	-
Composite outcomes	X	X	-	-	X	X
PROMs	X	X	X	X	X	X
HRQoL	X	X	X	X	X	X
Symp.reduct.	X	-	-	-	-	-
QALY	-	X	-	X	-	X
Biomarkers	X	-	X	-		

[a] IQWiG indicates in their guideline to perform health economic analysis, however, this is not common practice and therefore we excluded these result;

[b] The FDA allows this outcome to be included in the assessment for accelerated approval and regular approval;

[c] PFS and tumour response are recommended in the ICHOM standard set for colorectal cancer;

[d] RFS is discussed in the ICHOM standard set for breast cancer and colorectal cancer

Abbreviations: EUnetHTA European network for Health Technology Assessment; NICE the National Institute for Health and Care Excellence; ZIN the Dutch National Health Care Institute; IQWiG the Institute for Quality and Efficiency in Health Care; FDA Food and Drug Administration; EMA European Medicines Agency; ICHOM International Consortium for Health Outcomes Measurement; CEA Cost-Effectiveness Assessment; REA Relative Effectiveness Assessment; PFS Progression Free Survival; DFS Disease Free Survival; EFS Event Free Survival; TTP Time To Progression; RFS Regression Free Survival; PROMs Patient Reported Outcome Measures; HRQoL Health Related Quality of Life; Symp.reduct. Symptom Reduction; QALY Quality Adjusted Life Year.

IQWiG		FDA	EMA	ICHOM
Reimbursement		Market Approval	Market Approval	Value Based Healthcare
REA	CEA[a]			
X	-	X	X	X
X	-	X	X	X
X	-	X	X	X
X	-	X[b]	X	X
-	-	X[b]	X	X[c]
-	-	X[b]	X	-
-	-	-	X	-
-	-	X[b]	X	-
-	-	-	-	X[d]
-	-	X[b]	X	X[c]
X	-	X	-	-
X	-	X	X	X
X	-	X	X	X
X	-	X	X	X
-	-	-	-	-
X	-	X	X	-

Appendix 2. Hierarchy of outcomes accepted by EUnetHTA, NICE, ZIN, IQWiG, the FDA and the EMA

Institute	Primary outcomes	If primary outcome not available	Secondary outcomes
EUnetHTA	Long-term and definitive outcomes (mortality or survival), adverse reactions, PFS[d], HRQoLg	Validated intermediate outcomes, validated biomarkers, composite outcomes	Non-definitive outcomes (morbidity, function, HRQoL), ADRs
Life-threatening disease	Mortality or survival	Validated intermediate outcomes	Morbidity and/ or HRQoL
Non-life threatening disease	Morbidity, PROMs and HRQoL	Not mentioned	Not mentioned
First assessment	Definitive clinical outcomes (mortality and survival)	Validated intermediate outcomes, sufficiently large safety database	Not mentioned
Re-assessment	Definitive clinical outcomes on morbidity and mortality (stroke, fracture)	Not mentioned	Not mentioned
Economic evaluation	Life years gained, QALYs	Intermediate outcomes	Not mentioned
NICE	Survival, disease progression, HRQoL, PFS[d] or OS[d]	Intermediate outcomes on mortality and HRQoL	Not mentioned
Economic evaluation	QALY	Not mentioned	Not mentioned
ZIN	Clinically relevant outcomes (morbidity, mortality, EFS, PROMs, pain score, HRQoL), serious and frequent ADRs, toxicity, complications, PROMs[d], composite outcomes[d]	Intermediate outcomes	Any other health outcomes and side effects which are relevant
Economic evaluations	QALY, clinically relevant outcomes (increase in life expectancy, EFS)	Not mentioned	Not mentioned
IQWiG	Mortality, morbidity (symptoms and complications), HRQoL, validate intermediate outcomes, relevant ADRs, PROMs (disease symptoms)	Not mentioned	Diagnostic tests which are a precondition for assigning treatment

Appendix 2. Continued

Institute	Primary outcomes	If primary outcome not available	Secondary outcomes
FDA			
Regular approval	Survival improvement, OS, PROMs, intermediate outcomes, DFS, PFS, TTP, ORR, CR, improvement in physical functioning or tumour-related symptoms, time to progression of cancer symptoms, toxicity, improvement in DFS[d], durable complete response[d], substantiated ORR[d], TTP[f]	Not mentioned	Tumour measurement and response, PROMs, HRQoL, biomarkers
Accelerated approval	Intermediate outcomes, DFS, PFS, TTP, ORR, CR	Not mentioned	Not mentioned
EMA	Efficacy (survival), safety (tolerability and severe or life-threatening ADRs), TTP[d], PFS[d], time to symptomatic tumour progression[d]	Not mentioned	HRQoL, symptom deterioration, PROMs
Single agents & combination therapies	Cure rate, OS, PFS, DFS, event rate[d], symptom control[d], time to symptomatic progression[d]	Not mentioned	ORR, rate of tumour stability, symptomatic tumour progression, HRQoL, PROMs
Treatment with curative intent	PFS[b,d] ,DFS[e], EFS[b], ORR[b], increased cure rate[c], OS[c], EFS[d], CR[a,d], CR+PR[a,d], major increase ORR[b,d], major increase in EFS[c,d] or PFS[c,d]	Not mentioned	Not mentioned
Treatment intended to achieve long term disease control	PFS[a,b], improved survival[c], major benefit in PFS[c,d]	Not mentioned	Not mentioned
Palliative therapy	Prolonged OS, improved symptomatic control and HRQoL	Not mentioned	Not mentioned
Adjuvant therapy	Increased cure rate, OS, DFS[d], safety[d] and survival[d]	Not mentioned	CR

Appendix 2. Continued

Institute	Primary outcomes	If primary outcome not available	Secondary outcomes
Neo-adjuvant therapy	OS, PFS, DFS, enabling surgery and organ preservation	Not mentioned	Not mentioned

[a] When reduced or similar toxicity is expected
[b] When increased toxicity is expected
[c] When a major increase in toxicity is expected
[d] By exception this outcome may be used as primary outcome, this may be related to a specific patient population or treatment, for example for patients with solid tumours, in small populations, in the adjuvant setting, or in late line therapy
[e] When improved cure rate is the objective
[f] When the majority of deaths is unrelated to cancer
[g] HRQoL may be used as a primary outcome when the questionnaire was developed with the objective to capture the specific impact of a given pathology
[h] This outcome may by exception be used as primary outcome

Abbreviations: HTA Health Technology Assessment; EUnetHTA European network for Health Technology Assessment; NICE the National Institute for Health and Care Excellence; ZIN the Dutch National Health Care Institute; IQWiG the Institute for Quality and Efficiency in Health Care; FDA Food and Drug Administration; EMA European Medicines Agency; PROMs Patient Reported Outcome Measures; HRQoL Health Related Quality of Life; QALY Quality Adjusted Life Year; PFS Progression Free Survival; ADRs Adverse Drug Reactions; OS Overall Survival; DFS Disease Free Survival; TTP Time To Progression; ORR Objective Response Rate; CR Complete Response; EFS Event Free Survival; PR Partial Response;

Chapter 3

Bridging health technology assessment and healthcare quality improvement using international consortium of health outcomes measurement standard sets

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Abstract

Objectives: Although health technology assessment (HTA) and healthcare quality improvement are distinct processes, a greater level of alignment in outcome measures used may increase the quality and efficiency of data collection. This study evaluates the agreement in outcome measures used in oncology for healthcare quality improvement and HTAs, and how these align to the International Consortium for Health Outcomes Measurement (ICHOM) standard sets.

Methods: We conducted a cross-sectional comparative analysis of ICHOM sets focusing on oncological indications, and publicly available measures for healthcare quality and HTA reports published by the National Health Care Institute from the Netherlands and the National Institute for Health and Care Excellence from the United Kingdom.

Results: All ICHOM sets and HTAs used overall survival, while quality improvement used different survival estimates. Different progression estimates for cancer were used in HTAs, ICHOM sets and quality improvement. Data on health related quality of life (HRQoL) was recommended in all ICHOM sets and all HTAs, but selectively for quality improvement. In HTAs, generic HRQoL questionnaires were preferred while in quality improvement and ICHOM sets disease-specific questionnaires were recommended. Unfavourable outcomes were included in all HTAs and all ICHOM sets, but not always for quality improvement.

Conclusions: Although HTA and quality improvement use outcome measures from the same domains, a greater level of alignment seems possible. ICHOM may provide input on standardized outcome measures to support this alignment. However, residual discrepancies will remain due to the different objectives of HTA and quality improvement.

Introduction

Historically, health technology assessment (HTA) and improvement of healthcare quality are distinct processes. Where HTA has been focusing on the systematic evaluation of health technologies regarding its properties, effects and impact, and aims to inform policy decision-making,[1] while improving quality of healthcare has been important to ensure the proper use of the best available knowledge concerning the use of healthcare in order to improve health outcomes.[2] Although the purpose of these two worlds are distinct, they depend on each other and are in some cases closely aligned.[3] For example, similar data sources are used, where information from randomized clinical trials are important to inform HTA decision-making but are also used in the development of clinical guidelines for quality improvement.[4] Additionally, in HTA the use of real-world data, which may originate from clinical practice, is increasingly used to complement data from clinical trials and also provide input on quality of care.[5] This indicates that some overlap in the information used for quality improvement and HTA decision-making seems to exist.

In both HTA and quality improvement evidence traditionally focused in part on clinical data, including objective information on mortality and morbidity. However, patient reported outcome measures (PROMs) are becoming increasingly important in HTA[6] and in quality improvement,[7] since these capture outcomes which are relevant to patients and cannot be obtained through clinical measures. PROMs focus more on the patient perspective, including patients' perspective on adverse events (AEs) or how their health related quality of life (HRQoL) is affected due to their disease and/or treatment. The International Consortium for Health Outcomes Measurement (ICHOM) has developed so-called standard sets that contain lists of standardized outcomes, which they claim are relevant to patients, for a specific indication. These standard sets include both clinical data and PROMs. ICHOM could therefore be an initiative which could support further alignment between the worlds of quality improvement and HTA in healthcare.

To measure quality of care, three different types of measures can be distinguished, namely structure measures, process measures and outcome measures.[8] For quality improvement all three types of measures are important, however for HTA and in ICHOM standard sets outcome measures are most important and possibly most relevant to patients.[8] Therefore, to be able to determine whether further alignment may be possible between HTA and

quality of care we will need to focus on outcome measures. This study aimed to assess the agreement between outcome measures that are collected for quality improvement in healthcare and for HTAs, and how both align to the outcome measures recommended by ICHOM.

Methods

We conducted a cross-sectional comparative analysis of ICHOM standard sets, and publicly available healthcare quality measures and HTA reports published by two national healthcare institutes based in the Netherlands (NL) and United Kingdom (UK). We selected these institutes because they are both involved in healthcare quality improvement and conducting HTAs, which is currently rare in the rest of the western world. We specifically focused on oncology, due to the development of many new oncology treatments in recent years, the substantial uncertainty regarding the relevance of these treatments for patients, the increased toxicity which often accompanies these treatments, and the considerable costs for these treatments.

On January 10th 2020 a total of 5 ICHOM standard sets were identified that focus on oncological indications. These standard sets include colorectal cancer, breast cancer, lung cancer, localized prostate cancer, and advanced prostate cancer and can be accessed via the website of ICHOM (https://www.ichom.org/standard-sets/).

Quality measures are independently developed by the stakeholders involved, such as healthcare professionals and patients. These measures are subsequently published on the websites of both the Dutch National Health Care Institute (ZIN) and the National Institute for Health and Care Excellence (NICE). The most recently published quality measures on the websites of ZIN (www.zorginzicht.nl) and NICE (www.nice.org.uk) were extracted in March 2020 when these related to colorectal cancer, breast cancer, lung cancer and prostate cancer (Appendix 1). On the website for ZIN quality measures are described on the so called 'transparency calendar', while on the website for NICE quality measures are described in the quality standards published on the website. Since these quality measures have been developed by stakeholders, and not by ZIN or NICE, we will refer to these quality measures as published in the NL and UK.

Both ZIN and NICE conduct HTAs of drugs, but sometimes also of other health technologies such as diagnostics and medical devices, in order to support policy decision-making. To identify HTA reports the websites of ZIN and NICE were searched in January 2020. The following keywords were used: colon cancer, colorectal cancer, breast cancer, lung cancer, prostate cancer. The two most recent HTA assessments for colorectal cancer, breast cancer, lung cancer, and prostate cancer published by ZIN were extracted (Appendix 1). The corresponding HTA assessments published by NICE were subsequently collected. Both ZIN and NICE conduct a relative effectiveness assessment (REA) and a cost-effectiveness assessment (CEA). NICE conducts a CEA for each reimbursement assessment, while ZIN only conducts a CEA when the REA indicated an added value for the new drug. The objectives of a REA and CEA are different, where a REA focuses on establishing the net therapeutic benefit of an intervention [9] and a CEA allows prioritization of interventions based on the greatest improvement in health for the least cost.[10] Consequently, there may be a difference in the outcome measures used and have therefore been collected separately for the REA and CEA. In this study we refer to ZIN and NICE as HTA-NL and HTA-UK, respectively.

From all included ICHOM standard sets, quality measures and HTA reports data were extracted, and an overview of the outcome measures used was created. We considered the extraction of outcome measures to be straight forward, therefore, only one author (RK) was involved in creating this overview. From ICHOM standard sets all outcome measures recommended in the outcomes table were extracted. All outcome measures mentioned in each of the HTA reports were collected, separately for the REA and CEA sections of the report. Regarding quality measures, outcome measures for curative and palliative care were collected as well as outcome measures regarding patient satisfaction. Outcome measures used for quality improvement which focused on prevention (e.g. smoking cessation, public awareness) were excluded.

Results

The same survival estimate was recommended in all the ICHOM standard sets as used in all the HTAs, namely overall survival (Table 1). In addition, ICHOM recommended the collection of other survival data, such as cause of death and death attributed to breast cancer (Table 1). In the HTA for lung cancer the collection of post progression survival was additionally used (HTA-UK and HTA-NL). To measure quality improvement survival estimates were only suggested for breast cancer (quality-UK) and lung cancer (quality-NL and quality-UK), this included survival rates, mortality, and the percentage of deceased patients (Table 1).

Table 1. Survival estimates used for quality improvement (NL, UK), in HTA (NL, UK) and recommended by ICHOM standard sets

Outcome measure	**Quality Measure**		**HTA**				**ICHOM**[a]
	NL	**UK**	**NL**		**UK**		
			REA	**CEA**	**REA**	**CEA**	
Overall survival							
Breast cancer			X	X[b]	X	X	X
Lung cancer			X	X	X	X	X
Colorectal cancer			X	X	X	X	X
Prostate cancer			X	X	X	X	X
Survival rate							
Breast cancer		X					
Lung cancer		X					
Colorectal cancer							
Prostate cancer							
Cause of death							
Breast cancer							
Lung cancer							X
Colorectal cancer							X
Prostate cancer							
Other survival estimates							
Breast cancer		X[c]				X[d]	X[e]
Lung cancer	X[f]			X[g]		X[g]	X[h]
Colorectal cancer							
Prostate cancer							X[i]

[a] The standard sets of advanced and localized prostate cancer are reported under prostate cancer
[b] For the pharmaco-economic analysis of ZIN the assessment of palbociclib was used because the assessment of ribocliclib and abemaciclib referred to the cost-effectiveness of palbociclib [22]

[c] Information on the mortality from breast cancer was to be collected
[d] The proportion of deaths among PFS events and TTD was to be collected
[e] Information on death attributed to breast cancer was to be collected
[f] The percentage of patients deceased due to lung cancer within 30 days after resection and the percentage of patients with non-small cell lung cancer deceased during or within 90 days of being treated with concurrent chemoradiotherapy was to be collected
[g] Information on post progression survival was collected
[h] Information on treatment-related mortality was to be collected
[i] Information on cause-specific survival was to be collected
CEA, cost-effectiveness assessment; HTA, Health Technology Assessment; ICHOM, International Consortium of Outcome Measures; NICE, National Institute for Health and Care Excellence; NL, the Netherlands; REA, relative effectiveness assessment; UK, the United Kingdom; ZIN, National Health Care Institute.

Different estimates for progression were used in HTAs, ICHOM standard sets and for quality improvement (Table 2). In all HTA reports progression free survival was used, for both REAs and CEAs, which was also used in the ICHOM standard set for colorectal cancer. Additionally, time to progression was used in the HTAs for breast cancer (HTA-UK) and prostate cancer (HTA-NL). ICHOM recommended the collection of recurrence free survival for breast cancer and colorectal cancer, and several progression estimates for prostate cancer. As quality measure only in the UK the collection of progression estimates was suggested, specifically for breast cancer and colorectal cancer (Table 2). This included the proportion of people with rectal cancer with local disease recurrence and breast cancer recurrence.

Table 2. Progression estimates used for quality improvement (NL, UK), in HTA (NL, UK) and recommended by ICHOM standard sets

Outcome measure	**Quality Measure**		**HTA**				**ICHOM[a]**
	NL	**UK**	**NL**		**UK**		
			REA	**CEA**	**REA**	**CEA**	
PFS							
Breast cancer			X	X[b]	X	X	
Lung cancer			X	X	X	X	
Colorectal cancer			X	X	X	X	X
Prostate cancer			X	X	X	X	
RFS							
Breast cancer							X
Lung cancer							
Colorectal cancer							X
Prostate cancer							

Table 2. Continued

Outcome measure	Quality Measure		HTA				ICHOM[a]
	NL	UK	NL		UK		
			REA	CEA	REA	CEA	
Time to progression							
Breast cancer						X	
Lung cancer							
Colorectal cancer							
Prostate cancer			X				
Other progression estimates							
Breast cancer		X[c]					
Lung cancer							
Colorectal cancer		X[d]					
Prostate cancer							X[e]

[a] The standard sets of advanced and localized prostate cancer are reported under prostate cancer
[b] For the pharmaco-economic analysis of ZIN the assessment of palbociclib was used because the assessment of ribociclib and abemaciclib referred to the cost-effectiveness of palbociclib [22]
[c] Information on breast cancer recurrence was to be collected
[d] The proportion of people with rectal cancer with local disease recurrence was to be collected
[e] Information on the procedures needed for local progression, biochemical recurrence, development of metastasis, symptomatic skeletal event, and development of castration-resistant disease was to be collected

CEA, cost-effectiveness assessment; HTA, Health Technology Assessment; ICHOM, International Consortium of Outcome Measures; NICE, National Institute for Health and Care Excellence; NL, the Netherlands; PFS, progression free survival; REA, relative effectiveness assessment; RFS, recurrence free survival; UK, the United Kingdom; ZIN, National Health Care Institute

Data on Health Related Quality of Life (HRQoL) was recommended in all ICHOM standard sets and reported in all HTAs (Table 3). HRQoL was also suggested for quality improvement for breast cancer, colorectal cancer and prostate cancer for quality-NL, and for lung cancer for quality-UK. However, we observed a substantial difference between the use of generic and disease specific HRQoL questionnaires between HTA, quality measures and ICHOM. HTA agencies prefer generic HRQoL measures as these allow the calculation of utilities needed for CEAs. For the CEA of breast cancer and colorectal cancer generic HRQoL questionnaires were used, while for lung cancer and prostate cancer only disease specific HRQoL questionnaires were available. These disease specific questionnaires were used to calculate generic HRQoL utility values by using the method of mapping. For REAs, on the other hand, both data from generic and disease specific HRQoL questionnaires was used.

Table 3. Health Related Quality of Life questionnaires used for quality improvement (NL, UK), in HTA (NL, UK) and recommended by ICHOM standard sets

Outcome measure	Quality Measure		HTA				ICHOM[a]
	NL	UK	NL		UK		
			REA	CEA	REA	CEA	
EQ-5D							
Breast cancer			X	X[b]	X	X	
Lung cancer				X[c]	X	X[c]	
Colorectal cancer			X	X		X	
Prostate cancer				X[d]		X[d]	
EORTC QLQ-C30							
Breast cancer	X		X		X	X	X
Lung cancer					X		X
Colorectal cancer			X				X
Prostate cancer							X
Other generic HRQoL questionnaires							
Breast cancer					X		
Lung cancer			X				
Colorectal cancer			X		X		
Prostate cancer							
Other disease-specific HRQoL questionnaires							
Breast cancer	X		X		X	X	X
Lung cancer		X			X		X
Colorectal cancer	X						X
Prostate cancer	X		X		X		X

[a] The standard sets of advanced and localized prostate cancer are reported under prostate cancer
[b] For the pharmaco-economic analysis of ZIN the assessment of palbociclib was used because the assessment of ribociclib and abemaciclib referred to the cost-effectiveness of palbociclib [22]
[c] The EORTC QLQ-C30 and QLQ-LC13 were used to map EQ5-D utility values
[d] The FACT-P was used to map EQ5-D utility valuesCEA, cost-effectiveness assessment; EORTC QLQ-C30, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; EQ-5D, EuroQol-5 Dimension; HRQoL, health related quality of life; HTA, Health Technology Assessment; ICHOM, International Consortium of Outcome Measures; NICE, National Institute for Health and Care Excellence; NL, the Netherlands; REA, relative effectiveness assessment; UK, the United Kingdom; ZIN, National Health Care Institute.

HTAs preferred generic HRQoL for CEAs, whereas for quality improvement and, in all ICHOM standard sets, disease specific HRQoL questionnaires were preferred (Table 3). Disease specific questionnaires may be more sensitive in detecting change in HRQoL and allow a more detailed insight into specific

aspects relevant for a given disease. Often the disease specific HRQoL questionnaire recommended by ICHOM was also used in the clinical part of the HTAs and as quality measure, for example for breast cancer (Appendix 2). However, in ICHOM standard sets more questionnaires were recommended than used in HTAs or as quality measures, except for lung cancer where HTA-UK used three additional disease specific HRQoL questionnaires for HTA (Appendix 2). For lung cancer it was not stated which questionnaire should be used to collect information for quality improvement (quality-UK) or in HTA, specifically REA (HTA-NL). For quality improvement of colorectal cancer (quality-NL) it was also not stated which questionnaire should be used as quality measure.

Table 4. Information on unfavourable outcomes used for quality improvement (NL, UK), in HTA (NL, UK) and recommended by ICHOM standard sets

Outcome measure	**Quality Measure**		**HTA**				**ICHOM**[a]
	NL	**UK**	**NL**		**UK**		
			REA	**CEA**	**REA**	**CEA**	
Adverse Events[b]							
Breast cancer		X	X	X[c]	X	X	X
Lung cancer	X		X	X	X	X	X
Colorectal cancer			X		X	X	X
Prostate cancer	X		X	X	X	X	X
Treatment discontinuation							
Breast cancer			X		X	X	
Lung cancer			X	X	X	X	
Colorectal cancer			X				
Prostate cancer			X	X		X	
Other outcome measures							
Breast cancer					X[d]	X[d]	
Lung cancer							
Colorectal cancer							
Prostate cancer							

[a] The standard sets of advanced and localized prostate cancer are reported under prostate cancer
[b] In ICHOM standard sets and for quality improvement in the Netherlands it is recommended to collect information regarding complications
[c] For the pharmaco-economic analysis of ZIN the assessment of palbociclib was used because the assessment of ribociclib and abemaciclib referred to the cost-effectiveness of palbociclib [22]
[d] For breast cancer NICE also used information on the treatment emergent adverse events leading to deaths for the REA and safety measures for the CEACEA, cost-effectiveness assessment; HTA, Health Technology Assessment; ICHOM, International Consortium of Outcome Measures; NICE, National Institute for Health and Care Excellence; NL, the Netherlands; REA, relative effectiveness assessment; UK, the United Kingdom; ZIN, National Health Care Institute.

Adverse events or complications were included as outcome measures in the HTAs conducted by HTA-NL and HTA-UK, for both the REA and CEA, in ICHOM standard sets and as quality measure in the UK for breast cancer and in the NL for lung cancer and prostate cancer (Table 4). Information on treatment discontinuation was used by HTA-NL for the REAs of all included indications, while HTA-UK only used it in the REAs of breast cancer and lung cancer. Both HTA-NL and HTA-UK used treatment discontinuation in some CEAs, including breast cancer (HTA-UK), lung cancer (HTA-UK and HTA-NL), and prostate cancer (HTA-UK and HTA-NL). Treatment discontinuation was not recommended in any of the ICHOM standard sets, nor included as quality measure in either the NL or UK.

Other outcome measures were reported to a lesser extent, including response rate, margin status, resection, prostate-specific antigen, and patient satisfaction (Appendix 3). Information on resection, for example, was only mentioned for colorectal cancer as quality measure in the NL and UK, and in the HTAs of HTA-NL (CEA) and HTA-UK (REA and CEA), but not in the ICHOM standard set.

Discussion

Although there are differences in the specific outcome measures used in quality improvement and HTA, there is agreement in the domains applied. Information on survival, progression, HRQoL and unfavourable outcomes seem to be important in both HTA and quality improvement. Additionally, these domains are also incorporated in ICHOM standard sets, and therefore may potentially be important to patients. More specifically, both in HTA and ICHOM standard sets overall survival is used as survival estimate, this type of information is also important in quality improvement although different estimates are used. Different estimates for progression are used in HTA, quality improvement (quality-UK), and ICHOM standard sets. When assessing HRQoL there is some overlap in the disease specific HRQoL questionnaires used, however, only in HTA the use of generic HRQoL questionnaires is specified. Regarding unfavourable outcomes, the terms complications and AEs seem to be used interchangably. Although, there already is some alignment between HTA, quality improvement, and ICHOM, this may be further increased by using the same outcome measures for survival, progression and unfavourable outcomes. For example, while in HTA progression free survival is used for colorectal cancer,

ICHOM recommends recurrence free survival and as quality measure in the UK the proportion of people with local disease recurrence is suggested.

In a comparison between the outcome measures used for quality improvement in the NL and UK differences are apparent. For example, for breast cancer in quality-NL the collection of HRQoL estimates is suggested (Table 3), while for quality-UK the importance of AEs and patient satisfaction is stressed (Table 4 and Appendix 3). While for lung cancer, there is agreement between the two sets of quality measures on the importance of survival estimates (Table 1), but for quality-NL the collection of AEs is suggested as an addition (Table 4), whereas for quality-UK HRQoL and patient satisfaction are added (Table 3 and Appendix 3). We also show a difference in outcome measures between indications, where for instance resection estimates are suggested in both quality-NL and quality-UK for colorectal cancer, but not for any other indication included (Appendix 3). These differences may be indication specific or are due to a variety of stakeholders being involved in developing these quality measures, since stakeholders will have different insights, opinions and priorities.[11] Also the role of patients in development of quality measures may play a role, where some indications (e.g. breast cancer) may have more active patient organizations compared to others (e.g. lung cancer) or patient involvement may be limited.[12] This suggests that outcome measures used for quality improvement seem to be less standardized than those used in HTA. It also raises the question which outcome measures truly reflect patient preferences, as both ICHOM standard sets and measures for quality improvement have been developed with input from patient representatives.[12] Yet, the degree of convergence is not optimal.

This study closely relates to our previous research, comparing outcome measures used in regulatory guidelines, HTA guidelines and ICHOM standard sets, where we showed that outcome measures relevant to patients are also relevant for regulatory and reimbursement decision-making. However, some differences were apparent since in regulatory decision-making some outcome measures (e.g. intermediate outcomes) were more easily accepted than in reimbursement decision-making.[13] ICHOM standards sets, may therefore not only help align outcome measures used in regulatory and reimbursement decision-making, but also increase the alignment with outcome measures used for quality improvement. This could potentially benefit each process, as well as ensure information is used for multiple purposes.

Our previous study focused on outcome measures recommended in HTA and regulatory guidelines,[13] however, these may be different from the outcome measures actually available for decision-making. With regard to HTA, in the guidelines of HTA-NL and HTA-UK both overall survival and progression free survival are recommended. Our current study shows that both outcome measures were also provided in the HTA assessment. When focusing on HRQoL, both HTA-UK and HTA-NL recommend the use of the EQ-5D questionnaire in their guideline to conduct CEA. However, as shown in the current study this was not always available in practice. In those cases, both HTA-NL and HTA-UK used mapping methods to calculate the EQ-5D utility values using disease specific questionnaires. Regarding unfavourable outcomes, both HTA-UK and HTA-NL take these into account in their HTA decision-making, although this is not specifically mentioned in the HTA-UK guideline. In addition, when specific outcome measures are unavailable for HTA decision-making additional data collection may be requested to allow a re-assessment when more mature data is available, such as a recommendation within the Cancer Drugs Fund by HTA-UK. However, in practice HTA agencies seem to rely on the outcome measures which are available (e.g. PFS) to allow reimbursement decision-making, even when outcome measures recommended in their guidelines are unavailable (e.g. OS).

A limitation of this study is the focus on HTA-UK and HTA-NL, while other European countries also conduct HTAs and assess quality improvement. However, we think that this comparison is a valid start because in other countries HTA and assessing quality of care is done in different institutes which makes a comparison more challenging. In addition, it is important to note that other types of measures used to determine quality of care were excluded, i.e. structure measures and process measures. Although structure and process measures asses the value to patients regarding the organization of the care process, and are important to determine the quality of care, these aspects are generally not taken into account for HTA. To illustrate, structure measures may include 'the number of certified oncological surgeons working at the hospital location who treated breast cancer patient in the year of reporting', and process measures may include 'the proportion of people with rectal cancer who are offered a preoperative treatment strategy appropriate to their stage of local disease recurrence'. Since these measures are only relevant for quality improvement, we excluded these from our analysis. Finally, although we considered the extraction of outcome measures to be straightforward, having only one author involved in the extraction process could potentially lead to bias in the data collection.

One strength which can be identified in this study is the inclusion of ICHOM standard sets to assess outcomes which are believed to be relevant to patients. ICHOM standard sets indicate that several measures are important to collect, this includes measures regarding the case-mix, treatment and outcomes. For the purpose of this study we included all outcome measures (e.g. HRQoL, AEs, survival) reported in each ICHOM standard set. The extent to which these standard sets are patient relevant may be questioned, however, since some outcome measures recommended in ICHOM standard sets were developed with limited patient involvement.[14] In addition, it may be difficult to convert standardized outcome measures to routinely collecting these in practice,[15] yet ICHOM standard sets have been successfully implemented already.[16,17] Finally, other standardized sets of outcome measures, such as ICHOM, have been developed as well. These are often referred to as core outcome sets and are reported in the Core Outcome Measures in Effectiveness Trials Initiative (COMET) database. However, these core outcome sets are not always interchangeable. For example, in the COMET database the ICHOM standard set for breast cancer is reported which focuses on breast cancer in general.[18] Two other core outcome sets for breast cancer are also listed in the COMET database, but one specifically focuses on outcomes relevant for autologous fat grafting in breast reconstruction and another on laboratory biomarkers.[19,20] Some core outcome sets from the COMET database are comparable to the ICHOM standard sets, such as for localized prostate cancer, where some similarities and differences are apparent. More specifically, both the ICHOM standard set and one other core outcome set recommend collecting information on OS and urinary function for example, but only the ICHOM standard set recommends outcomes related to bowel irritation and hormonal symptoms whereas the other core outcome set recommends anxiety and depression outcomes.[21,22] Such differences may be due to involvement of different stakeholders or stakeholders from different countries.

We observed a difference between the use of generic and disease specific HRQoL questionnaires. HTA agencies generally prefer generic measures to conduct CEAs, however, when unavailable for an assessment HTA agencies may use mapping methods to calculate utilities based on disease specific questionnaires.[10] HTA agencies do not prefer these mapping methods due to several methodological issues.[10] It may, however, be possible to improve such methods or develop new methods to calculate utilities based on disease specific questionnaires.[23] This would further increase the level of alignment, since ICHOM and quality improvement mainly recommend the use of disease specific measures. Alternatively, generic HRQoL measures may also be included

in ICHOM standard sets and for quality improvement. However, these processes have different contexts and purposes which may necessitate some differences in the outcome measures used. Our results show a multitude of disease specific HRQoL questionnaires recommended in ICHOM standard sets, which may increase respondent burden.[24] Developing a way to limit the number of questionnaires, but retaining the same level of reliability may be an option to mitigate this. Our results also show that in some cases a few questions from a specific questionnaire were recommended, such as the recommendation to use single items of the FACT-ES for breast cancer by ICHOM, which may play a part in solving this. It is, however, unclear why only a few questions were selected and whether this would be sufficient to actually measure HRQoL. When HTA, quality improvement and ICHOM more often recommend the same HRQoL questionnaires it may contribute to an evidence ecosystem where the same outcome measures are used by several stakeholders.

Developing an evidence ecosystem is important to reduce costs, resources and burden of registration in healthcare, as well as increase the relevance and reliability of evidence collected. It is envisioned that decision support, including guidelines and HTAs, will support clinicians, patients and policy-makers in decision-making, but also inform implementation and evaluation of healthcare improvement.[4,25] In addition, data accrued from clinical practice is more often being used in HTAs as complementary evidence,[5] and the same type of data could inform quality improvement as well as other parts of the evidence ecosystem. A greater level of alignment is imperative, however, to ensure data from clinical practice only needs to be collected once and allow its use for several purposes. This may only be possible with a greater collaboration between the HTA and quality improvement societies. In addition, quality improvement may benefit from increasing consistency between outcome measures used for different oncological indications, especially when these outcome measures seem important for patients (e.g. survival, progression, unfavourable outcomes and HRQoL) and therefore are arguably also important to assess regarding quality of care. Some discrepancies may remain due to the different objectives of healthcare quality improvement and HTA. These different objectives, however, seem to justify the need of outcome measures from the same domains for HTA and quality improvement. Therefore, since outcome measures from the same domains seem important for both quality improvement and HTA a greater level of alignment may be possible. ICHOM could provide input on standardized outcome measures to support an evidence ecosystem, where quality improvement and HTA make use of the same evidence.

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Authorship Statement

RK designed the study in collaboration with the co-authors. RK collected and analysed the data, and wrote the draft manuscript. All co-authors actively contributed throughout the conduct of the study and critically reviewed and approved the manuscript.

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Appendices

Appendix 1. Overview of publicly available documents on quality measures available in the Netherlands and the United Kingdom and HTA assessments published by ZIN and NICE included in this study

Breast Cancer		
Type of document	**Institute**	**Document name**
HTA	ZIN	Abemaciclib (Verzenios®) for the treatment of metastatic breast cancer
HTA	NICE	Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA579); Abemaciclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (TA563)
HTA	ZIN	Ribociclib (Kisqali®) for the treatment of metastatic breast cancer
HTA	NICE	Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (TA496)
QM	NL[a]	Transparency calendar for medical specialist care 2020, and indicators factsheet breast cancer audit 2020
QM	UK[b]	Breast cancer quality standard

Lung cancer		
Type of document	**Institute**	**Document name**
HTA	ZIN	Durvalumab (Imfinzi®) fort he treatment of locally advanced, unresectable, non-small-cell lung cancer
HTA	NICE	Durvalumab for treating locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation
HTA	ZIN	Osimertinib (Tagrisso®) for first line treatment of patients with advanced or metastatic EGFR mutation-positive non-small-cell lung cancer
HTA	NICE	Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer
QM	NL[a]	Transparency calendar for medical specialist care 2020, and indicator guide lung cancer 2020
QM	UK[b]	Lung cancer in adults quality standard

Year published	Indication	Drug
2019	Hormone receptor positive, HER2-negative advanced or metastatic breast cancer	Abemaciclib
2019	Hormone receptor positive, HER2-negative advanced breast cancer	Abemaciclib
2017	Metastatic breast cancer	Ribociclib
2017	Hormone receptor positive, HER2-negative locally advanced or metastatic breast cancer	Ribociclib
2019	Primary breast cancer, including ductal carcinoma in situ, invasive carcinoma, paget's disease, inflammatory breast cancer, tumors of all stages including distant metastasis. Excluding lobular carcinoma in situ, recurrent breast cancer, phyllodes tumours and non-surgically treated patients	N/A
2011, last updated 2016	Early (ductal carcinoma in situ and evasive), locally advanced and advanced breast cancer, recurrent breast cancer and familial breast cancer in adults	N/A

Year published	Indication	Drug
2019	Locally advanced unresectable NSCLC	Durvalumab
2019	Locally advanced unresectable NSCLC	Durvalumab
2018	Advanced or metastatic NSCLC	Osimertinib
2020	Untreated EGFR mutation-positive NSCLC	Osimertinib
2019	Lung cancer	N/A
2012, last updated 2019	Lung cancer	N/A

Appendix 1. Continued

Colorectal cancer		
Type of document	**Institute**	**Document name**
HTA	ZIN	Cetuximab (Erbitux®) for the treatment of metastatic colorectal cancer (re-assessment)
HTA	NICE	Cetuximab and panitumumab for previously untreated metastatic colorectal cancer (TA439)
HTA	ZIN	Panitumumab (Vectibix®) for the treatment of metastatic colorectal cancer
HTA	NICE	Cetuximab and panitumab for previously untreated metastatic colorectal cancer
QM	NL[a]	Transparency calendar for medical specialist care 2020, and indicator guide colorectal cancer 2020
QM	UK[b]	Colorectal cancer quality standard
Prostate cancer		
Type of document	**Institute**	**Document name**
HTA	ZIN	Abirateron (Zytiga) for the treatment of castration-resistant metastatic prostate cancer
HTA	NICE	Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen
HTA	ZIN	Cabazitaxel (Jevtana®) for the treatment of metastatic prostate cancer
HTA	NICE	Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel
QM	NL[a]	Transparency calendar for medical specialist care 2020, and indicator guide prostate cancer 2020
QM	UK[b]	Prostate cancer quality standard

[a] Available from: www.zorginzicht.nl

[b] Available from: www.nice.org.uk/standards-and-indicators

CEA, cost-effectiveness assessment; EGFR, Epidermal Growth Factor Receptor; HER2, Human Epidermal growth factor Receptor 2; HTA, Health Technology Assessment; ICHOM, International Consortium of Outcome Measures; N/A, Not Applicable; NICE, National Institute for Health and Care Excellence; NL, the Netherlands; NSCLC, non-small cell lung cancer; QM, Quality Measure; REA, relative effectiveness assessment; UK, the United Kingdom; ZIN, National Health Care Institute.

Year published	Indication	Drug
2017	Metastatic colorectal cancer	Cetuximab
2017	Previously untreated metastatic colorectal cancer	Cetuximab & panitumumab
2015	Metastatic colorectal cancer	Panitumumab
2017	Metastatic colorectal cancer	Panitumumab
2019	Including all primary colorectal carcinoma, for which part of the colon or rectum has been resected. All primary rectal tumours undergoing the watchful waiting strategy (also without resection). Excluding resections, dysplastic polyps, sarcoma, carcinoid tumours, melanomas, gastrointestinal stromal tumours, lymphoma, and loco-regional or distant recurrences of a colorectal carcinoma.	N/A
2012, last updated 2020	Colorectal cancer (colon cancer and rectal cancer)	N/A

Year published	Indication	Drug
2012	Metastatic castration resistant prostate cancer	Abiraterone
2016	Metastatic castration resistant prostate cancer	Abiraterone
2011	Metastatic prostate cancer	Cabazitaxel
2016	Metastatic prostate cancer	Cabazitaxel
2019	Prostate cancer	N/A
2015, last updated 2019	Prostate cancer	N/A

Appendix 2. Overview of specific Health Related Quality of Life questionnaires used for quality improvement (NL, UK), in HTA (NL, UK) and recommended by ICHOM standard sets

Outcome measure	**Quality Measure**		**Health Technology Assessment**	
	NL	**UK**	**NL**	
			REA	**CEA**
Breast cancer				
Generic			EQ-5D	EQ-5D
Disease specific	EORTC QLQ-C30		EORTC QLQ-C30	
	EORTC QLQ-BR23		EORTC QLQ-BR23	
	BREAST-Q			
Lung cancer				
Generic			HRQoL (unspecified)	EQ-5D[b]
Disease specific				
		HRQoL for adults with lung cancer (unspecified)		
Colorectal cancer				
Generic			EQ-5D	EQ-5D
			Increase in HIS	
Disease specific			EORTC QLQ-C30	
	Percentage of patients participated in the PREM oncology questionnaire			

Health Technology Assessment		ICHOM[a]
UK		
REA	CEA	
EQ-5D	EQ-5D	
BPI short form (pain intensity)		
EORTC QLQ-C30	EORTC QLQ-C30	EORTC QLQ-C30
EORTC QLQ-BR23 (safety and breast cancer module)		EORTC-QLQ-BR23
		BREAST-Q
	Breast cancer module	EORTC QLQ-LMC21 (single item)
		FACT-ES (single items)
EQ-5D	EQ-5D[b]	
EORTC QLQ-C30		EORTC QLQ-C30
EORTC QLQ-LC13		EORTC QLQ-LC13
EORTC QLQ-LC12		
CTSQ-16		
PRO-CTCAE		
	EQ-5D	
HRQoL (unspecified)		
		EORTC QLQ-C30
		EORTC QLQ-CR29
		MSKCC bowel function – dietary subscale
		EORTC QLQ-LMC21 (single item)

Appendix 2. Continued

Outcome measure	Quality Measure		Health Technology Assessment	
	NL	UK	NL	
			REA	CEA
Prostate cancer				
Generic				EQ-5D[c]
Disease Specific	EPIC-26 (minimally questions 5 and 18)			
			Pain intensity score, pain medication score, reduction of pain intensity measured using BPI-SF	

[a] The standard sets of advanced and localized prostate cancer are reported under prostate cancer
[b] The EORTC QLQ-C30 and QLQ-LC13 were used to map EQ5-D utility values
[c] The FACT-P was used to map EQ5-D utility values
BPI, Brief Pain Inventory; BPI-SF, Brief Pain Inventory Short Form; BREAST-Q, Breast Cancer Questionnaire; CEA, cost-effectiveness assessment; CTSQ-16, Cancer Therapy Satisfaction Questionnaire; EORTC, the European Organization for Research and Treatment of Cancer; EPIC-26, Expanded Prostate Cancer Index Composite 26;
EQ-5D, EuroQol-5 Dimension; FACT-ES, Functional Assessment of Cancer Therapy Endocrine Symptoms; FACT-P, Functional Assessment of Cancer Therapy Prostate;
HRQoL, health related quality of life; HTA, Health Technology Assessment; ICHOM, International Consortium of Outcome Measures; MSKCC, Memorial Sloan-Kettering Cancer Center; NICE, National Institute for Health and Care Excellence; NL, the Netherlands; PRO-CTCAE, Patient Reported Outcomes Common Terminology Criteria for Adverse Events; QLQ-BR23 Quality of Life Questionnaire Breast Cancer 23; QLQ-C30, Quality of Life Questionnaire Cancer 30; QLQ-CR29 Quality of Life Questionnaire Colorectal Cancer 29; QLQ-LC12 Quality of Life Questionnaire Lung Cancer 12; QLQ-LC13 Quality of Life Questionnaire Lung Cancer 13; QLQ-LMC21 Quality of Life Questionnaire Colorectal Liver Metastases 21; QLQ-PR25 Quality of Life Questionnaire Prostate Cancer 25; REA, relative effectiveness assessment; UK, the United Kingdom; ZIN, National Health Care Institute.

Health Technology Assessment		ICHOM[a]
UK		
REA	CEA	
	EQ-5D[c]	
		EPIC-26
Pain progression		Use of over the counter pain medication or strong pain medication
QoL FACT-P		EORTC QLQ-PR25
		Additional questions from the Utilization of Sexual Medications/ Devices questionnaire

Appendix 3. Other outcome measures used for quality improvement (NL, UK), in HTA (NL, UK) and recommended by ICHOM standard sets

Outcome measure	Quality Measure		HTA				ICHOM[a]
	NL	UK	NL		UK		
			REA	CEA	REA	CEA	
Response rate of tumour							
Breast cancer					X	X	
Lung cancer			X		X		
Colorectal cancer			X		X		X
Prostate cancer			X				
Margin status							
Breast cancer							X
Lung cancer							
Colorectal cancer							X
Prostate cancer							
Patient satisfaction							
Breast cancer		X					
Lung cancer		X					
Colorectal cancer							
Prostate cancer		X					
Other							
Breast cancer							
Lung cancer							X[b]
Colorectal cancer	X[c]	X[c]		X[c]	X[c]	X[c]	X[d]
Prostate cancer	X[e]		X[e]		X[e]		

[a] The standard sets of advanced and localized prostate cancer are reported under prostate cancer
[b] Information on the duration of time spent in hospital at the end of life was to be collected
[c] Information on resection was collected
[d] Information on hospital admission at the end of life and stoma status was to be collected
[e] Information on PSA values was collected

CEA, cost-effectiveness assessment; HTA, Health Technology Assessment; ICHOM, International Consortium of Outcome Measures; NICE, National Institute for Health and Care Excellence; NL, the Netherlands; REA, relative effectiveness assessment; UK, the United Kingdom; ZIN, National Health CareInstitute.

Part B

Possibilities of social media to contribute to health technology assessment recommendations

Chapter 4

Use of Social Media in the Assessment of Relative Effectiveness: Explorative Review With Examples From Oncology

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Abstract

Background: An element of health technology assessment constitutes assessing the clinical effectiveness of drugs, generally called relative effectiveness assessment (REA). Little real-world evidence is available directly after market access, therefore randomized controlled trials are used to obtain information for REA. However, there is growing interest in using real-world data (RWD) for REA. Social media may provide a source of RWD.

Objective: We assessed the extent to which social media-generated health data has provided insights for REA.

Methods: An explorative literature review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify examples in oncology where health data were collected using social media. Scientific and grey literature published between January 2010 and June 2016 was identified by four reviewers, who independently screened studies for eligibility and extracted data. A descriptive qualitative analysis was performed.

Results: Of 1032 articles identified, eight were included: four articles identified adverse events in response to cancer treatment, three articles disseminated quality of life (QoL) surveys, and one study assessed the occurrence of disease-specific symptoms. Several strengths of social media-generated health data were highlighted in the articles, such as efficient collection of patient experiences and recruiting patients with rare diseases. Conversely, limitations included validation of authenticity and presence of information and selection bias.

Conclusions: Social media may provide a potential source of RWD for REA, particularly on aspects such as adverse events, symptom occurrence, QoL, and adherence behavior. This potential has not yet been fully realized and the degree of usefulness for REA should be further explored.

Introduction

Within the context of rising healthcare costs, limited budgets, and the onslaught of innovative yet expensive medications, the value of health technology assessment (HTA) for decision-makers, regulators, pharmaceutical companies and patients is becoming increasingly important. HTA is defined as "the systematic evaluation of the properties and effects of a health technology".[1] Health technologies are defined as "interventions developed to prevent, diagnose or treat medical conditions, promote health, provide rehabilitation, or organize healthcare delivery".[2] An important element of HTA is relative effectiveness, i.e. the extent to which an intervention – provided under routine clinical conditions – does more good than harm in comparison to one or more alternatives.[1] Traditionally, a relative effectiveness assessment (REA) conducted directly after market authorization of a new drug is extrapolated using health outcomes (e.g. mortality) obtained from randomized controlled trials (RCTs), which are often considered the gold standard for this type of analysis. However, the tightly-controlled conditions and highly selective patient groups within RCTs may result in findings that are not generalizable to routine clinical settings where patients are more heterogeneous. In routine practice, pregnant women, children, elderly people and patients with comorbidities may eventually receive the new drugs examined in RCTs, while these patient populations are generally excluded from such RCTs. Therefore, researchers may additionally resort to real-world data (RWD) as a supplementary source of evidence to assess relative effectiveness. Real-world data can be defined as "an umbrella term for data regarding the effects of health interventions that are not collected in the context of conventional randomized controlled trials".[1] Patient registries and electronic health records are established examples of RWD sources, but another potential source of RWD may be social media.

Social media are often used by patients as a source to search for information on their health conditions, share their experiences and find social support.[3,4] For example, many patients use Twitter to stay up to date with the latest healthcare developments and increase their knowledge on their disease, while Facebook is more often used for social support and exchanging experiences.[3] Social media users who have a chronic condition are more likely to use the internet for such purposes than are healthy social media users.[5] By assessing the content viewed, generated and exchanged by patients through social media, a considerable amount of information on patient perspectives and experiences can be gathered.

Although social media have been used for different aspects of research, such as patient recruitment,[6-8] dissemination of interventions[9,10] and education,[11] little is known about its contribution to REA.

In 2008 a study showed that blogs could be used to collect patient experiences regarding diabetes and diabetes management to provide information for HTA by enhancing the evidence available in published literature.[12] More recently, several pharmaceutical companies have begun to make use of social media to gain insight into patient perspectives on adverse events (AEs)[13,14] and to assess their switching behaviors.[15] Similarly, the Association of the British Pharmaceutical Industry (ABPI) has published guidelines on best practices for the monitoring and management of AEs through such sources.[16] Moreover, the Food and Drug Administration (FDA) is increasingly focusing on the use of health data from social media by collaborating with PatientsLikeMe; a platform where patients can share their health data online to gain insight into patient perspectives on adverse events.[17,18] Considering these initiatives, it may become possible for health data reported by patients on social media to contribute to the REA of new therapies.

The aim of this article is to assess the extent to which health data generated from social media have provided insights for REA. We conducted an explorative review to identify examples in oncology where health data were collected using social media. Oncology was chosen due to the considerable number of innovative drugs being developed at a rapid pace in this area. For example, the European Medicines Agency reported in 2015 that one-third of the medicines with a new active substance recommended for market access were for cancer treatment.[19] As mentioned earlier, REAs of drugs are traditionally based on health outcomes such as overall survival and progression-free survival. However, considering the often-marginal differences in overall survival and progression-free survival for oncological drugs, information on AEs, adherence and quality of life is becoming even more important in REA.[20] Collecting these aspects from RCTs can be difficult, therefore other data sources such as social media may be useful. For the purposes of this explorative review, social media were defined as "a group of Internet-based applications that allow the creation and exchange of user-generated content".[21]

Methods

An explorative review was performed based on the PRISMA guidelines.[22] To identify scientific literature, a search for peer-reviewed published articles was carried out in MEDLINE through the PubMed interface for the period between 1 January 2010 and 28 June 2016 on June 28th, 2016. The following search query was used:

(Facebook[tiab] OR Twitter[tiab] OR blog[tiab] OR blogging[mesh] OR "social media"[tiab] OR ehealth[tiab] OR e-health[tiab] OR "online community"[tiab] OR "online communities"[tiab] OR "online patient"[tiab] OR "health data"[tiab] OR (online [tiab] AND research[tiab] AND platform[tiab]) OR (personal*[tiab] AND health[tiab] AND record*[tiab]) OR (online[tiab] AND patient[tiab] AND communit*[tiab]) OR (online[tiab] AND data[tiab] AND shar*[tiab])) AND (oncolog*[tiab] OR cancer[tiab] OR carcinoma[tiab] OR metast*[tiab] OR neoplasms[mesh] OR melanoma[tiab] OR tumor[tiab] OR tumour[tiab]).*

The reference lists from the literature, which were included based on title and abstract, were hand-searched to identify additional literature. To extend the literature search, the top four health informatics journals according to SCImago Journal and Country Rank[23] were included, namely GigaScience, BMC Medical Research Methodology, Open Bioinformatics Journal, and Journal of Medical Internet Research. The websites of these health informatics journals were hand-searched by assessing theme issues and by using the following keywords: "oncology, cancer, carcinoma, metastasis, neoplasm, tumor, tumour, blog, blogging, social media, e-health, online or health data".

A Google search was conducted in July and August 2016 to identify grey literature, such as relevant websites, by combining the following keywords: "social media", "online patient", "online research platform", "relative effectiveness", "health research", "effectiveness research", "pharmacovigilance", "adherence", and "to measure quality of life". Before each search, the history of the browser was cleared to ensure findings would not be influenced by previous search queries. Due to the vast number of websites retrieved through the Google search, only websites that collect health data online, focus on patient-reported outcomes, or provide online information on drugs and conditions were deemed relevant for further analysis. The selection of relevant websites was also based on consensus between the authors RK and RtH. These websites were

hand-searched to identify grey literature by browsing through the website in search of relevant reports or documents and by using the following keywords: “social media”, “internet”, “Facebook”, “Twitter”, “pharmacovigilance” or “health research”. These keywords were different from those used for the Google search due to the character of the platform (ie, a Google search is inherently different from searching a website). The following websites were included: PatientsLikeMe, Microsoft HealthVault, Dossio, CureTogether, WhatNext, MyGly, Drug Information Association, WEB-RADR, National Patient-Centered Clinical Research Network, College ter Beoordeling van Geneesmiddelen, Handle My Health, European Alliance for Personalized Medicine, Lareb, WHO Monitoring Centre for Pharmacovigilance Uppsala, PEW Research Center, Social Media Research Foundation, Treato, MediGuard, Healthy.me, and iVitality.

The review was conducted by four reviewers (RK, AM, RtH and KM) and the resulting literature was independently screened by the reviewers for eligibility. The titles and abstracts from scientific literature were assessed by RK, AM and KM, while grey literature was assessed by RK and RtH. Literature was considered eligible for inclusion when it was: 1) published between 1 January 2010 and 28 June 2016, 2) available in English, 3) examples were provided where social media were used to collect health data, 4) literature focused on cancer or cancer treatment, and 5) literature was either a peer-reviewed original research article or a report that was available in the public domain. We excluded literature that did not meet all inclusion criteria. Relevant full articles and reports were retrieved and reviewed for inclusion.

Two reviewers (RK and AM) independently extracted data from all included articles and reports using a predefined data abstraction form. Information on study characteristics (e.g. study design, study period, type of social media used), and the strengths, limitations and acceptability of using social media to generate health data were extracted. Disagreements in data extracted were resolved by consensus amongst RK and AM.

A descriptive qualitative analysis of the extracted data was carried out, since the topics, methods and outcomes of included literature were notably diverse.

Results

A total of 2351 citations were identified from scientific literature (n=879), a hand search of reference lists from scientific literature (n=56), grey literature (n=97), and a hand search of health informatics journals (n=1319). From these, a total of 2290 citations were excluded based on title or abstract, additionally 26 duplicates were excluded. Of the 35 full scientific publications and documents assessed, 27 were excluded: 15 citations did not provide an example of health data collection, nine were not oncology-specific, and three provided insufficient information on the collection of health data. Data were abstracted from a total of eight scientific publications (Figure 1).

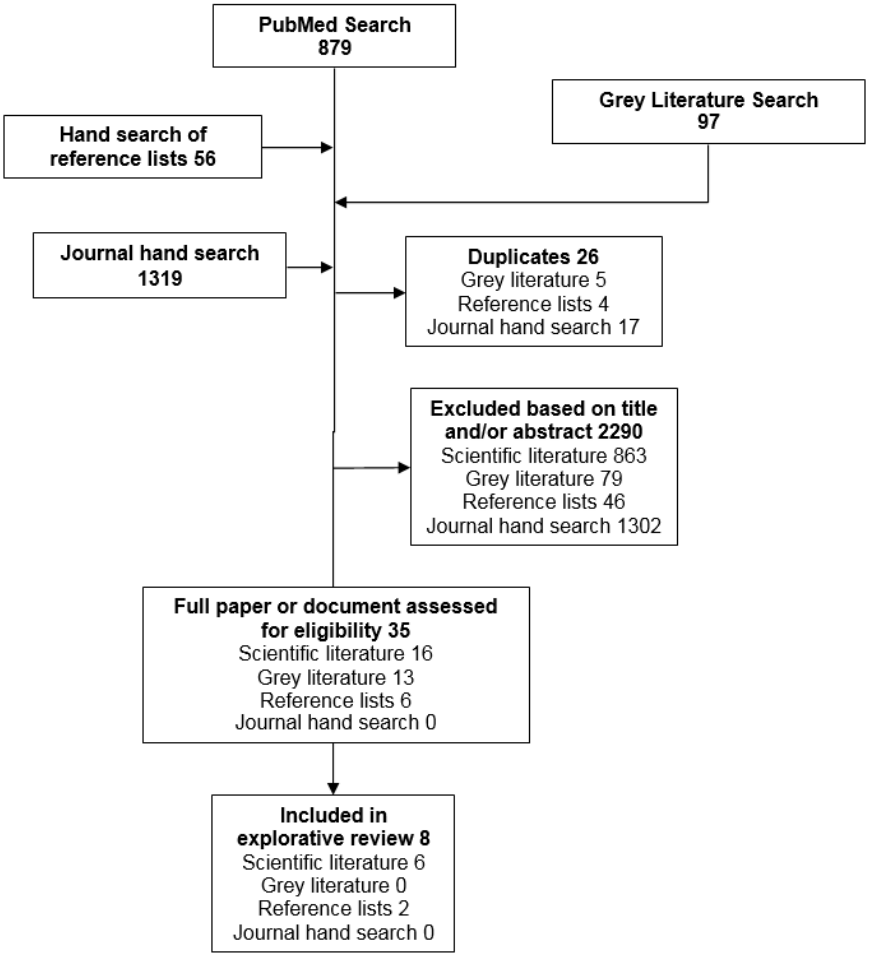

Figure 1. Flowchart of the literature review process

Table 1 provides an overview of the eight scientific publications included. Different types of cancer and medications were assessed in each of the publications. The focus of all eight articles was testing the feasibility and added value of generating health data from social media, such as AEs, QoL, adherence, symptom occurrence and experience from social media.

Table 1. Overview of included scientific publications

Study	Aim	Cancer Type	Drug
Beusterien 2013 [24]	To better understand patient experience with CCC in the real-world setting	Colorectal cancer	Chemo-therapeutic agents
Freifeld 2014 [25]	To evaluate the level of concordance between Twitter posts mentioning AE-like reactions and spontaneous reports received by a regulatory agency	N/A	Methotrexate[a]
van der Heijden 2016 [26]	To investigate whether we could use crowdsourcing via Facebook and online surveys for medical research purposes on PVNS	Pigmented villonodular synovitis	N/A
McCarrier 2016 [27]	To explore the feasibility of using social media-based patient networks to gather qualitative data on patient-reported outcome concepts relevant to CLL	Chronic lymphocytic leukaemia	N/A
Mao 2013 [28]	To understand frequency and content of AE's and associated adherence behaviours discussed by breast cancer patients related to using AI	Breast Cancer	Aromatase inhibitors
Marshall 2015 [29]	To identify and examine symptom patterns generated by data extracted from a breast cancer forum, and compare these findings to an analysis of symptoms reported by breast cancer survivors enrolled in a research study and who responded to a symptom checklist	Breast Cancer	N/A
Pages 2014 [30]	To describe the characteristics of AE's reported by patients exposed to OAN agents in an online discussion, and compare these with those reported by health professionals as recorded in the French pharmacovigilance database	Cancer	OAN agents
Zaid 2014 [31]	To determine the feasibility of using social media to perform cross-sectional epidemiologic and QoL research on patients with rare gynaecologic tumours	Neuroendocrine carcinoma of the cervix	N/A

[a] This study assessed adverse events reported in social media for a total of 23 drugs and 4 vaccines, including 1 drug (methotrexate) specific for oncology.

CCC, colorectal cancer chemotherapies; AEs, adverse events; N/A, not applicable; PVNS, pigmented villonodular synovitis; CLL, chronic lymphocytic leukaemia; AI, aromatase inhibitors; OAN, oral antineoplastic; QoL, quality of life.

Table 2. Study characteristics of included scientific publications that use social media to collect health data

Study	Study design	Study period	Posts analysed	Number of respondents	Type of social media used to collect health data	Type of health data collected
Beusterien 2013 [24]	Cross-sectional	52 days	1522 posts	264	2 disease specific forums	AEs, physical functioning & emotional impacts
Freifeld 2014 [25]	Retrospective	7 months	6,900,000 posts	N/A	Twitter	AEs
van der Heijden 2016 [26]	Prospective	70 months	N/A	272	Facebook (patient community)	Socio-demographic factors, disease- specific characteristics[a], functional outcome, and QoL
McCarrier 2016 [27]	Cross-sectional	4 months	N/A	50	Online patient platform	Socio-demographic factors, disease- specific characteristics[b], experience of symptoms, perceptions about treatment, and QoL
Mao 2013 [28]	Retrospective	8 years	1,235,400 posts	N/A	12 disease- specific forums	AEs and adherence
Marshall 2015 [29]	Retrospective	8 years	50,426 posts	12,991	1 disease- specific forum	Symptom occurrence, co-occurrence, and similarity index of 25 pre-selected symptoms.
Pages 2014 [30]	Retrospective	1 year	111 posts	66	5 health forums	AEs
Zaid 2014 [31]	Cross-sectional	30 days	N/A	57	Facebook (support group)	Socio-demographic factors, disease- specific characteristics[c], and QoL

[a] Disease-specific characteristics include clinical presentation, findings on imaging and biopsy material, type and localization of disease, surgical and adjuvant treatment, local recurrences, and post-operative complications.

[b] Disease-specific characteristics include self-reported current chronic lymphocytic leukaemia stage, performance status, and past and current treatment.

[c] Disease-specific characteristics include clinical presentation, initial work-up, treatments, past and current disease status, follow-up, and recurrence pattern.

AEs, adverse events; N/A, not applicable; QoL, quality of life.

Table 2 shows that publications differed substantially in study design, study period, the number of posts analysed and the number of respondents included in the analysis. Forum topics and discussions were assessed in four papers, in two studies a survey was posted on the Facebook page of either a patient community or support group, in one study Twitter conversations were assessed and in one study an online patient platform was used to disseminate a survey. Of the eight studies, a total of four studies collected health data on AEs. [24,25,28,30] More specifically, three of these publications presented the AEs identified on the forums included,[24,28,30] while the fourth publication focused on comparing AEs mentioned online to AEs reported to the FDA.[25] Another three studies collected health data on quality of life (QoL).[26,27,31] Each study used different QoL instruments, such as the Concerns About Recurrence Scale scores,[31] and short form-36 health survey.[26] Finally, one study focused on identifying symptom (co-) occurrence.[29] In addition to the main outcome measures, van der Heijden et al, McCarrier et al, and Zaid et al collected data on socio-demographic factors and disease specific characteristics.[26,27,31] Furthermore, Beusterien et al collected health data on physical functioning and emotional impacts,[24] and Mao et al collected information on adherence by mapping decisions about continuing or stopping treatment.[28]

The four publications that used forums to collect health data varied substantially in the explanation for their forum selection (Table 3). For example, Beusterien et al used two search engines and two different computers for their forum search which they repeated every other day for two weeks. Additionally, they used selection criteria to include the two forums (ie, site active >5 years, >12,000 posts on forum, >20 individuals currently browsing, and >10 new posts per day).[24] Meanwhile, Marshall et al selected one forum without clarifying selection criteria for the selected forum.[29] The other four publications, making use of Twitter, Facebook or an online patient platform, selected this social media platform due to the access of a large volume of health data[25] or access to a patient community.[26,27,31] Regarding the use of automated processes to collect health data from social media, two publications specifically indicated to have used a web crawler[28,29] and one publication made use of the Twitter application programming interface.[25] Two of the included publications indicated to have collected all the forum posts related to search terms without specifically indicating the collection method used[24,30] and three publications used the social media platform to distribute a survey.[26,27,31] Automated techniques were used by Freifeld et al, Mao et al and Marshall et al to analyse the health data collected.[25,28,29] Freifeld et al used a tree-based dictionary-matching algorithm to identify specific text from the forum posts collected, and furthermore used a Natural Language Processing (NLP) semi-automated classifier

to identify AEs.[25] Mao et al also used NLP to identify AEs,[28] and Marshall et al used NLP in a data mining algorithm to identify symptoms.[29] The remaining five publications made use of content analysis,[24,27] descriptive or quantitative analysis (e.g. chi-squared test),[26,31] or labelled forum posts manually.[30]

Table 3. Selection of social media platform and use of automated techniques by included literature that use social media to collect health data

Study	Clear explanation for selection of social media platform	Web crawler used for collecting social media health data	Automated technique used for analysis of health data
Beusterien 2013 [24]	Yes	No	No
Freifeld 2014 [25]	Yes	No[a]	Yes
van der Heijden 2016 [26]	Yes	No[b]	No
McCarrier 2016 [27]	Yes	No[b]	No
Mao 2013 [28]	Yes	Yes	Yes
Marshall 2015 [29]	No	Yes	Yes
Pages 2014 [30]	Yes	No	No
Zaid 2014 [31]	Yes	No[b]	No

[a] The Twitter application programming interface (API) was used to identify relevant tweets.
[b] A survey was distributed via the social media platform.

In Table 4 the strengths and limitations of health data generated through social media that were identified in the eight included publications are presented. Five publications identified the ability to assess patient perspectives as an important strength.[24,25,28-30] The ability to access patients who have rare diseases or are distributed over wide geographic areas was considered a major strength by five publications.[26-29,31] Furthermore, Freifeld et al, Marshall et al and Pages et al emphasized that social media should complement conventional (pharmacovigilance) methods, since a difference between results from social media and conventional methods may be present.[25,29,30] For example, patients were shown to report different AEs compared to health professionals who traditionally provide this information.[30] Other strengths identified included the efficient collection of patient-reported outcomes,[24] the short time-period needed to survey patients,[29,31] and the identification of new or unlabelled AEs.[30]

Limitations of social media-generated health data mainly focused on validating authenticity, selection bias, information bias, and the inability to actively probe patients for responses. Validating authenticity focuses on the difficulty of verifying the accuracy of information provided through social media,[26,29] such as verifying whether posters have the disease[27,31] or are indeed on the drugs[24,27] they discuss. Regarding selection bias, publications reported differences in the patient population that use social media compared to those who do not; for example, patients using social media are conventionally more highly educated,[24,29] are more likely to be female,[26,27] may have a different symptom experience,[28] and are generally younger.[27,29,31] With regards to information bias, Freifeld et al and Pages et al reported duplication of posts,[25,30] Mao et al reported multiple posts by the same patients,[28] and Freifeld et al indicated that patients may not identify AEs correctly.[25] Finally, several publications mentioned the inability of using social media to actively probe patients for responses.[24,27,29] For example, patients may use alternative wording than that which researchers anticipate, which could lead to misclassifying symptom experiences.[29]

Regarding the acceptability of using social media to generate health data, Pages et al indicated that pharmaceutical companies are already using this type of data to gather information on AEs from patient perspectives.[30] Furthermore, Beusterien et al indicated that in patient-reported outcomes research, patient perspectives are commonly accepted with regards to disease and treatment impact,[24] and both Freifeld et al and van der Heijden et al noted the importance of insights into the patient perspective provided by social media research for regulatory authorities.[25,26] However, Freifeld et al was also cautious on the use of social media to generate health data.[25] Reasons for their caution was the need to still establish its role in pharmacovigilance as social media are not yet used in routine surveillance. Additionally, they indicated that data acquisition from social media and automation need to be improved.

Table 4. Strengths and limitations specific to the use of social media to generate health data

Study	Strengths	Limitations
Beusterien 2013 [24]	Patient perspective; Efficient and comprehensive collection of PROMS;	Validating authenticity: Selection bias; No active probing of patient responses; Incomplete information of sample;
Freifeld 2014 [25]	Patient perspective; Complementary to pharmacovigilance; Rapid information on AEs;	Information bias; Volume of posts; Noisy data;
van der Heijden 2016 [26]	Access to patients with rare diseases; Collection of PROMS; Convenient to fill in; Long-term follow-up	Validating authenticity; Selection bias; Low participation rate;
McCarrier 2016 [27]	Alternative approaches to qualitative data collection; Support development of PRO instruments; Access to patients with rare diseases; Motivated patients; Lower costs per enrolled patient	Validating authenticity; Selection bias; No active probing of patient responses; Not achieving concept saturation; Larger sample sizes needed;
Mao 2013 [28]	Patient perspective; Access to patients distributed over wide geographic areas; Increased generalizability due to more diverse patient population; Observed frequency key AEs reflected those reported in traditional studies	Selection bias; Information bias; Frequency data is not an indication of prevalence AEs;
Marshall 2016 [29]	Vast quantities of data; Easily accessible information; Short time-period; Access to patients with rare diseases; Low costs; Patient perspective; Complementary to traditional studies	Validating authenticity; Selection bias; Noisy data; No active probing of patient responses; Incomplete information of sample; Data quality or format inadequate; Ethical considerations; Misinterpretation of posts;
Pages 2014 [30]	Patient perspective; Complementary to pharmacovigilance; Identification new/unlabelled AEs	Information bias;
Zaid 2014 [31]	Access to patients with rare diseases and that are distributed over wide geographic areas; Short time-period; Motivated patients;	Validating authenticity; Selection bias;

PROMS, patient-reported outcome measures; AEs, adverse events; PRO, patient-reported outcomes.

Discussion

This explorative review demonstrates that, within the field of oncology, social media could be used for assessing AEs by collecting health data from forums and to evaluate QoL through Facebook or online patient platforms. Social media provides an opportunity to efficiently assess patient perspectives and collect health data from patients with rare diseases that are distributed over wide geographic areas. However, validating the authenticity of health data from social media is difficult, and is prone to selection and information bias. Furthermore, this type of data should be used complementary to traditional forms of research. Finally, this review provides additional insights, compared to reviews that focus on social media to inform pharmacovigilance,[32,33] by focusing on the use of social media to inform relative effectiveness assessments.

Arguably, the results found in this review on social media-generated data in oncology may not be generalizable to other fields of medicine, since different types of health data, social media or analysis may be of importance in other fields of medicine. However, many studies conducted in fields of medicine other than oncology similarly focused on identifying AEs,[32-38] suggesting our results are at least partially generalizable. Although little is known about assessing QoL through social media in other fields of medicine, there is potential for this mode of health data collection since QoL is often difficult to measure in RCTs and observational studies.[20] Finally, as our results show, another aspect of relative effectiveness that may be assessed through social media is treatment-switching and adherence behavior. A few pharmaceutical companies have been assessing this aspect already, thus demonstrating its potential.[14,15,39] Given the possibility of social media to generate data on AEs, QoL, and treatment-switching and adherence behavior, there is a great potential for social media-generated health data to enrich REA by incorporating information on these aspects.

One caveat of using social media to collect health data that requires special attention is the lack of clear methodological guidance. Standardized approaches to collecting health data from social media are necessary to ensure comparability and reproducibility between studies. For example, posts may either be extracted manually or by automated processes. The interpretation of these posts could also be done manually or by automated processes. However, some argue that automated processes may be unable to successfully interpret sarcasm in text posted on social media,[25] while others argue that automated natural language processing could assist in analysing the vast amounts of data available on social media.[33,40,41]

Another methodological issue involves the use of correct search terms, as posts may include misspellings, non-medical terms, and slang.[25,33,42] Additionally, several studies reported important methodological limitations to consider when assessing data from social media, which include validating authenticity (e.g. posts may be not genuine),[43-45] selection bias (e.g. social media users may differ in age, gender, ethnicity and physical location compared to non-users)[42,44,45] and information bias (e.g. patients may be taking a specific drug but fail to report the drug or its effects).[43,45] To manage these methodological limitations, it is important to systematically assess the risk of bias to determine the quality of the health data collected through social media. Extracting relevant health data from social media may be difficult and challenging due to the issues described above. Clear and uniform methodological guidance may improve the extraction, interpretation and subsequent use of social media to collect health data. An additional caveat that may hamper the use of social media for collecting health data for REA is the perceived risk of easy manipulation. A recent example of manipulation in social media was the circulation of fake news on social media during the 2016 elections in the United States of America.[46-48] These kind of examples affects the ability of social media users to discern what is true and correct information. However, although manipulation may occur, many still use social media to find information and to exchange experiences. Therefore, harnessing and analysing the vast amount of health data available on social media remains important.

Although caveats can be recognized in the use of social media-generated health data, the added value of collecting information on patients' perspectives and experiences towards relative effectiveness (e.g. AEs, quality of life, switching-behaviour) should be highlighted. For example, health data collected through social media may uncover AEs that occur after long-term use of new drugs, or they may detect AEs earlier compared to traditional methods,[44,49] or provide insights that are not available in published literature (e.g. diabetes patient experiences with laser therapy).[12] Additionally, social media may be a better source to identify AEs that are mild or symptom-related compared to more traditional methods.[44] However, health data collected through social media should be used in conjunction with traditional methods to ensure the collection of a comprehensive overview of aspects that can provide information for REA.

Important for the comprehensiveness of this review is that we assessed both academic and grey literature, which minimizes the possibility of missing important insights. Additionally, we ensured the quality of the review through

data abstraction conducted by two authors, which allowed a better substantiation of deductions made.

One limitation of this review was the focus on oncology, which may have resulted in missing literature on other aspects related to REA that could potentially be collected using social media. For example, PatientsLikeMe, an online patient platform that allows patients to share health data or exchange experiences on conditions and medications, published a few studies on the effectiveness of off-label drug use.[43,50] Additionally, PatientsLikeMe published a study focused on assessing the impact of menopause on disease severity in patients with multiple sclerosis.[51] These types of data may contribute to providing information for REA. The focus on oncology in this review was deemed appropriate since many new drugs are developed in the field of oncology, studies that assess these new drugs can be small and incomplete, and the European Medicines Agency and the European Network for Health Technology Assessment are also putting focus on the assessment of oncological drugs.

A second limitation relates to the search strategy employed in this explorative review. Firstly, the broad definition of social media that was used in this review may not allow for differentiating between passively collecting data (e.g. by collecting posts from a forum) and actively collecting data (e.g. by posting a survey on Facebook). There may be a difference in the information available from passively collecting information that patients discuss and post on social media, compared to actively posing questions to these patients in a survey. Secondly, by employing one database for our scientific and grey literature search we may have missed studies published in relevant journals that are not indexed by PubMed or grey literature that was not identified by the Google search engine. To overcome this limitation to some extent, we hand-searched the reference lists of included studies, based on title and abstract, and identified a few articles that had not been captured in the PubMed and Google search.

Social media may be a potential source of RWD for REA, particularly on aspects such as AEs, occurrence of disease-specific symptoms, adherence behaviour, and QoL. This potential has not yet been fully realized due to methodological limitations that accompany social media-generated health data, like information bias and selection bias, as well as the limited acceptability of such data. However, the degree of usefulness of such data for relative effectiveness assessment should be further explored. Moreover, methodological guidelines and tools should be developed to address the limitations mentioned above.

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Authorship Statement

RK designed the study in collaboration with the co-authors. RK screened the literature together with authors AM, RtH and KM. RK collected the data together with author AM. RK subsequently analysed the data, and wrote the draft manuscript. All co-authors actively contributed throughout the conduct of the study and critically reviewed and approved the manuscript.

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Chapter 5

Social media as a tool for assessing patient perspectives on quality of life in metastatic melanoma: a feasibility study

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Abstract

Purpose: Development of innovative drugs for melanoma is occurring rapidly. Incremental gains in overall survival amongst innovative products may be difficult to measure in clinical trials, and their use may be associated with increased toxicity profiles. Therefore, HTA agencies increasingly require information on HRQoL for the assessment of such drugs. This study explored the feasibility of social media to assess patient perspectives on HRQoL in melanoma, and whether current cancer- and melanoma-specific HRQoL questionnaires represent these perspectives.

Methods: A survey was distributed on the social media channels of Melanoma Patient Network Europe to assess melanoma patients' perspectives regarding HRQoL. Two researchers independently conducted content analysis to identify key themes, which were subsequently compared to questions from one current cancer-specific and two melanoma-specific HRQoL questionnaires (i.e. EORTC QLQ-C30, EORTC QLQ-MEL38, FACT-M).

Results: In total, 72 patients and 17 carers completed the survey. Patients indicated that family, having a normal life, and enjoying life were the three most important aspects of HRQoL for them. Carers indicated that being capable, having manageable adverse events, and being pain-free were the three most important aspects of HRQoL for patients. Respondents seem to find some questions from HRQoL questionnaires relevant (e.g. 'Have you felt able to carry on with things as normal?') and others less relevant (e.g. 'Have you had swelling near your melanoma site?'). Additionally, wording may differ between patients and HRQoL questionnaires, whereby patients generally use a more positive tone.

Conclusions: Social media may provide a valuable tool in assessing patient perspectives regarding HRQoL. However, differences seem to emerge between patient and carer perspectives. Additionally, patient perspectives did not seem to fully correlate to questions posed in cancer- (i.e. EORTC QLQ-C30) and melanoma-specific (i.e. EORTC QLQ-MEL38, FACT-M) HRQoL questionnaires examined.

Introduction

Health Technology Assessment (HTA) entails the systematic evaluation of the properties and effects of health technologies, addressing their direct and intended effects, as well as their indirect and unintended consequences with the aim of informing decision-making.[1] In multiple jurisdictions, manufacturers of (new) health technologies need to provide evidence that their product is of equal- or additional benefit to those currently available in order to qualify for reimbursement. Public or private HTA agencies then conduct an HTA of a submission (i.e. dossier of evidence) provided by the manufacturer to assess the (additional) benefit of the health technology. Subsequently, national, regional or local decision-makers (such as Ministries of Health, national payers or local payers) will use this HTA for their decision on reimbursement. Such HTA assessments can encompass several aspects of the implementation of health technologies in clinical practice such as their relative effectiveness, cost-effectiveness or appropriate use.[1] Relative effectiveness is defined as the extent to which an intervention does more good than harm, when compared to one or more alternative interventions for achieving the desired results and when provided under the routine setting of healthcare practice.[2]

Within the field of oncology, the development of innovative yet expensive therapeutic drugs is occurring at a rapid pace. Metastatic Melanoma provides an example where 8 novel therapies and 3 combination therapies, which belong to three new therapeutic classes, have gained market authorisation since 2011.[3,4] One positive consequence of the increased number of treatments has been the general prolongation of overall survival of metastatic melanoma patients.[3,4] However, provided that incremental gains in overall survival associated with innovative products may be difficult to measure in the context of clinical trials, and the toxicity profiles associated with their use may be considerable, HTA agencies increasingly require information on health-related quality of life (HRQoL) experienced by patients during the prolonged periods of survival as a means to assess the added value of innovative products within relative effectiveness assessments (REA).[5-7]

Conventionally, HRQoL of patients is measured using validated questionnaires that can be generic (e.g. EQ-5D),[8] disease-specific (e.g. EORTC-QLQ-30 or FACT-M)(9;10) or that include additional individualised measures.[11] From an HTA perspective, HRQoL data generated by generic questionnaires offers the advantage of allowing for comparison of health gains across disease areas

(e.g. oncology vs. chronic pulmonary diseases). Meanwhile, data acquired through disease-specific questionnaires aims to distinguish between HRQoL experienced at different stages of a particular disease (e.g. metastatic melanoma), thus possibly identifying medical need per disease stage. Therefore, HRQoL data can contribute to HTA as primary or secondary health outcomes for relative effectiveness data or as sources for utility values used in cost-utility analyses of new oncologic treatments.[5-7]

However, despite HTA guidance encouraging the collection of HRQoL data for HTA submissions, it is seldom included in submissions. Recent research in 6 different European jurisdictions has shown that HRQoL data features in only a third of HTA submissions for oncological treatments, with limited impact on decision-making for a number of reasons, including its sheer scarcity.[5] In addition, the available validated HRQoL questionnaires, whether generic or disease-specific, generally show low completion rates by patients, despite a generally prevailing notion of the importance of HRQoL.[12-14]

The IMI-GetReal initiative is a 3-year public-private partnership exploring the use of Real-World Evidence (RWE) in early drug development and drug assessment,[15] including a series of case studies. Here presented is our case study on metastatic melanoma where the potential of social media as a new source of RWE for HTA was investigated within a pilot literature review.[12,16] This research demonstrated the potential value of using social media to inform several parameters of HTA in oncology, including: adverse events,[12,17-19] treatment adherence[18] and HRQoL.[12,20-22]

Building upon results from this pilot review, this article aims to explore the use of social media as a tool to gather melanoma patients´ perspectives on HRQoL. More specifically, this article will: assess the comparability of the melanoma patient population accessible via social media with the general melanoma population, evaluate what melanoma patients and carers perceive as important in relation to HRQoL and compare this to validated cancer-specific HRQoL questionnaires, and assess whether current melanoma-specific HRQoL questionnaires represent melanoma patients' perspectives on HRQoL. It is important to emphasize that this is a feasibility study, aiming to advance the science of using social media to gain insights on patients' perspectives on HRQoL, rather than conducting a robust quantitative analysis to answer pre-defined hypotheses based on data collected through social media.

Methods

Members of Melanoma Patient Network Europe (MPNE),[23] an established patient network for melanoma patients, carers and advocates, were approached via multiple social media channels of MPNE to anonymously complete a web-based survey. An announcement with a brief description of the survey goals and link to the survey was posted on the private MPNE Facebook group, MPNE LinkedIn group, and MPNE twitter account. Members of MPNE were also approached by sending a single e-mail to the MPNE mailing list and by posting the announcement and link to the survey on the website of MPNE. Respondents were eligible for inclusion in the study if they self-reported a diagnosis of melanoma on the online survey or reported to be carer of a melanoma patient.

The web-based survey was conducted using Survey Monkey, and once a member clicked on the survey link it was presented on a separate screen. The survey was open for 30 days from January 8th 2016. Two reminders of the ongoing survey were posted on MPNE's private Facebook group, LinkedIn group, and Twitter account throughout the 30 day period. Respondents gave their informed consent by completing the survey. According to the 1964 declaration of Helsinki and its later amendments as well as with the ethical standards of Dutch law,[24] no official approval of an Ethical committee was necessary.

The web-based survey included 25 items (see Appendix 1). Socio-demographic and clinical characteristics were collected, including gender, country of residence, age, educational level, years since melanoma diagnosis, stage of disease, treatments received and patient-reported HRQoL. Patient and carer perspectives on HRQoL were explored by asking several open questions, including:

- What is HRQoL in melanoma for you?
- Name the 3 things that deteriorate your/ the melanoma patient's HRQoL today?
- Name the single thing that would improve your/ the melanoma patient's HRQoL right now?

To assess the comparability and generalizability of our study population to the general melanoma population, we compared socio-demographic variables to reported values in the literature.[25-27] A comparison of educational level was made by using the study of Eriksson et al.,[25] where all Swedish patients diagnosed with an invasive cutaneous malignant melanoma between 1990 and

2007 were included. Patients had a median age of 62 years at diagnosis. The age distribution in our study was compared to data available from the EORTC QLQ-C30 reference values,[26] these reference values are based on responses from a total of 223 stage I and II melanoma patients and 585 of stage III and IV melanoma patients. The gender distribution in our study was compared to that reported by Bay et al.,[27] where all skin melanoma patients registered in the Danish Cancer Register (1989 – 2011) were included. Additionally, we compared the overall quality of life reported in the EORTC QLQ-C30 reference values for melanoma patients to the overall quality of life reported by our study population. The question in our survey was similar to the question in the EORTC QLQ-C30, namely 'On a scale from 1 (poor) to 7 (excellent), please rate your/ the patient's Quality of Life today (see Appendix 1).

In order to evaluate what patients and carers regard important for HRQoL, two researchers independently performed inductive content analysis on the responses to the open-ended questions posed in the survey.[28] Content analysis allows for the organisation and cataloguing of respondent's descriptions of key aspects regarding melanoma patient views on HRQoL. Assigned codes and the grouping of similar codes were reviewed by both researchers and any discrepancies in coding were resolved by consensus. We present the results of the content analysis in two ways. First, we constructed a top 10 of aspects that are most often mentioned by patients and carers. This provides an insight of what patients and carers deem most important in melanoma patients HRQoL. Second, we created a word cloud based on the frequency generated codes were cited (either by patients or carers) to illustrate which aspects in HRQoL are most often mentioned by patients and carers. A word cloud visually represents the frequency words are mentioned in the text analysed, the more often a word is mentioned the larger in size it will be in the word cloud.[29,30]

To assess the extent to which current cancer-specific HRQoL questionnaires represent melanoma patients' perspectives on HRQoL, respondents were asked to rate the relevance of questions from the EORTC QLQ-C30 on a 5-point Likert scale, ranging from "not relevant at all" to "very relevant". The percentage of responses were then calculated per question; stratified for patients per disease stage and including a separate stratum for carers. The EORTC QLQ-C30 is a 30-item questionnaire that assesses the HRQoL of cancer patients and has been translated and validated in 41 languages. This cancer-specific HRQoL questionnaire can be used in conjunction with specific modules that allow the evaluation of HRQoL in specific patient populations (e.g. melanoma, breast cancer, lung cancer).[31]

To assess the relevance of questions in two melanoma-specific HRQoL questionnaires to respondents, namely EORTC MEL-38 and FACT-M, we performed a qualitative comparison of the key aspects identified during the content analysis and compared these to the questions posed in the melanoma-specific HRQoL questionnaires. This made it possible to assess to what extent our study population considered the questions in melanoma-specific HRQoL questionnaires relevant. The EORTC MEL-38 is a 38-item questionnaire that is being developed in a cross-cultural setting and should be used in conjunction with the EORTC QLQ-C30, but has not been validated yet.[32] The FACT-M is a tool including 24 items encompassing three HRQoL domains (i.e. physical well-being, emotional well-being, and social well-being)[33] and has been validated in a population of Stage I to Stage IV melanoma patients.[34]

Subgroup analyses were performed for patients and carers separately and were stratified by disease stage when possible. All data were coded, stored and analyzed using R version 4.00.03.05.[35]

Results

A total of 96 respondents completed the web-based survey. Of these 70 indicated to be patients, 17 were carers of a melanoma patient, 2 indicated to be both patients and carers, and 7 did not report either and were therefore excluded from the analyses. The 2 respondents indicating to be both patients and carers were included in the analysis as patients only. Patients who responded to the survey represented all stages of melanoma; 25% reported to have stage I, 14% reported to have stage II, 22% reported to have stage III, and 39% reported to have stage IV melanoma. Of the carers who responded to the survey, 6% cared for a patient who had stage I, none cared for a patient with stage II melanoma, 24% cared for a patient who had stage III, and most cared for a patient who had stage IV melanoma (71%). All analyses were stratified by stage for patients, however this was not possible for carers due to the small number of respondents.

Most respondents accessed the survey via Facebook (77%), Twitter was used to a lesser extent (2%). Some respondents accessed the survey via the MPNE website (9%) or the MPNE mailing list (1%). Finally, 11% of respondents indicated to have used other online channels linked to the MPNE, such as the Berlin Support Group, Melanoma Romania Association, and Dutch Melanoma Association Forum. The response rate for Facebook was 11%, MPNE had 695 Facebook

members and a total of 74 filled in the survey. We were unable to calculate response rates for the other sources on which the survey was distributed, because of the low number of respondents using other social media channels, or social media channels for which we did not possess the relevant information in order to calculate the response rate.

The socio-demographic characteristics of the study population are shown in Table 1. Respondents were mostly female (70%), between 35 and 64 (82%), were university graduates or higher (64%), and originated from the United Kingdom (50%). The paper of Bay et al. showed that approximately 50% of patients with melanoma in Denmark were female[27]; when stratified it was shown that 74% of patients in our study population were female whereas 53% of carers in our study population were female. The distribution of age in our study population was similar for most stages of melanoma and between carers and patients, except for patients with stage III where half of the respondents indicated to be between 55 and 64. The EORTC reference values also showed that the distribution of age was similar between stage I & II and stage III & IV, and were comparable to the age distribution found in our study population.[26] Compared to the educational level reported in the paper by Eriksson et al., where only 25% of melanoma patients in Sweden had a high education (e.g. a college degree or higher), our study sample was more highly educated with 64% having an university degree or higher.[25]

Table 2 shows that more than 60% of the patients with stage II, III, and IV melanoma indicated to have been diagnosed more than 2 years ago, compared to 44% of patients with stage I. A total of 65% of the carers indicated to take care of a patient who had been diagnosed more than 2 years ago. Most patients with stage II, III and IV melanoma as well as the carers who responded to the survey indicated that the patient had been diagnosed with cutaneous melanoma. Cutaneous melanoma had been diagnosed in 44% of patients with stage I melanoma, while 50% had been diagnosed with ocular, uveal or choroidal melanoma, and 6% of these patients didn't know the type of melanoma they had been diagnosed with. Most patients with stage I, II, or III melanoma indicated to be unfamiliar with any mutations present in their tumour, compared to 46% of patients with stage IV melanoma and 53% of carers who indicated that a BRAF mutation had been found in the tumour. Surgery was the treatment most often received by patients according to 92% of patients and carers in this study.

The overall HRQoL values reported by our study population are comparable to that reported by the EORTC as reference values for melanoma patients for the EORTC QLQ-C30 (Table 3).[26] Both stratified and non-stratified overall HRQoL values were similar, indicating that the HRQoL in our study population is similar to that in the general melanoma population.

Figure 1 shows the most often mentioned aspects by patients and carers in our study sample that are of influence to the patients' HRQoL. 'Family' was the single most often mentioned aspect while the second most often mentioned aspect relevant to melanoma patients' HRQoL was 'Normal Life', implying that patients find it highly important to lead a normal life while being ill. In Table 4 a more detailed analysis is shown whereby the top 10 most often mentioned aspects that influence melanoma patients' HRQoL is presented. It can be seen that patients themselves most often mentioned 'Family' as most important in their HRQoL, together with 'Good Care' by patients with stage I melanoma, 'Fear' by patients with stage II melanoma, 'Worry' by melanoma patients with stage III, and 'Good medicines' and 'Normal Life' by patients with stage IV melanoma. Carers mentioned 'Capability', 'No Adverse Events', and 'Pain free' most often as important aspects to patients' HRQoL. The second most often mentioned aspect by carers was 'Family', which indicates that patients and carers may have a different perspective regarding what is of most influence in patients' HRQoL.

Figure 1. Key aspects patients find important in QoL

Table 1. Socio-demographic characteristics of the study population, for each variable the percentages are calculated per stage

	Patients (n=72)			
	Stage I (n=18)	**Stage II (n=10)**	**Stage III (n=16)**	**Stage IV (n=28)**
Gender				
Male	17%	30%	25%	32%
Female	83%	70%	75%	68%
Age				
18-24	-	-	-	4%
25-34	6%	10%	13%	4%
35-44	22%	20%	13%	29%
45-54	28%	30%	25%	36%
55-64	33%	30%	50%	18%
65-74	6%	10%	-	7%
>75	6%	-	-	4%
Highest educational level				
Did not attend school	-	-	-	-
Finished school after primary school	-	-	-	-
Graduated from secondary school	11%	20%	25%	7%
Graduated from college	22%	10%	31%	21%
Graduated with university degree level	50%	60%	38%	50%
Higher degree or doctorate	17%	10%	6%	21%
Country of Residence				
Belgium	-	-	-	11%
France	-	-	-	4%
Germany	17%	10%	13%	-
Ireland	-	-	6%	11%
Italy	-	-	6%	-
Netherlands	-	-	6%	7%
Norway	6%	20%	13%	7%
Other‡	17%	-	6%	4%
Romania	11%	10%	-	7%
UK	50%	60%	50%	50%

* Three socio-demographic characteristics of our study population are compared to results from 3 scientific publications, namely gender[27], age[26], and educational level[25];

- no respondents ticked this answer (e.g. 0%);

†In this reference it is given that in Sweden low education corresponds to mandatory school, intermediate to high school, and high to college/university;

‡ 5 respondents originated from the USA and 1 respondent from Serbia.

Carers (n=17)		Reference Patient Population*			
		Stage I	**Stage II**	**Stage III**	**Stage IV**
47%	Male	43%	52%	56%	58%
53%	Female	57%	48%	44%	42%
		Stage I&II	**Stage III&IV**		
6%	<40	25%	27%		
12%	40-49	23%	26%		
24%	50-59	24%	23%		
29%	60-69	22%	18%		
24%	70-79	5%	6%		
6%	80+	1%	0%		
-					
		All Patients	**Female**	**Male**	
-	Low education†	36%	36%	36%	
-	Intermediate education	39%	39%	39%	
12%	High education	25%	25%	25%	
29%					
35%					
24%					
6%					
6%					
-					
-					
-					
24%					
-					
6%					
18%					
41%					

Table 2. Clinical characteristics of the study population, for each variable the percentages are calculated per stage

	Patients (n=72)				**Carers (n=17)₸**
	Stage I (n=18)	**Stage II (n=10)+**	**Stage III (n=16)***	**Stage IV (n=28)**	
Melanoma diagnosis					
< 1 month ago	-	-	-	-	-
1-3 months ago	6%	-	-	-	-
3-6 months ago	17%	-	7%	4%	-
6-12 months ago	28%	10%	13%	11%	6%
1-2 years ago	6%	20%	7%	25%	29%
2-5 years ago	22%	50%	40%	43%	24%
> 5 years ago	22%	20%	33%	18%	41%
Type of Melanoma					
Cutaneous melanoma	44%	70%	57%	64%	62%
Ocular/ Uveal/ Choroidal melanoma	50%	10%	7%	18%	12%
Acral melanoma	-	-	-	-	6%
Mucosal melanoma	-	-	-	-	-
I don't know	6%	20%	36%	18%	19%
Melanoma mutations					
BRAF mutant	11%	20%	27%	46%	53%
BRAF wild-type	-	-	-	18%	18%
NRAS mutant	-	-	-	7%	-
c-kit mutant	-	-	-	4%	6%
GNAQ/GNA11	-	-	7%	4%	-
I don't know	78%	60%	67%	11%	18%
None	6%	10%	-	4%	6%
Other‡	6%	10%	-	7%	-
Treatments received¥					
Surgery	89%	90%	94%	89%	100%
Radiotherapy	39%	20%	13%	39%	26%
Chemotherapy	-	11%	6%	25%	21%
Immune Therapies	-	-	25%	81%	56%
Targeted Therapies	-	-	6%	27%	50%

+ The total number of respondents on treatments received (chemotherapy) was 9;

* The total number of respondents on melanoma diagnosis is 15, on type of melanoma is 14, melanoma mutation is 15, and on treatments received is 15;

† Carers provided disease specific characteristics for the patient they care(d) for;

‡ Other melanoma mutations mentioned by 4 respondents were mutations in chromosome 3, 6 and/or 8;

₸ The total number of respondents on type of melanoma is 16, on treatments received is 16;

- no respondents ticked this answer (e.g. 0%);

¥ The percentage for 'treatments received' could be more than 100% because patients may have received more than one treatment;

NA: Not Applicable

Table 3. Overall quality of life in the study population compared to the EORTC reference value for the EORTC QLQ-C30

	Overall quality of life						
	1	**2**	**3**	**4**	**5**	**6**	**7**
Respondents: Stage I & II (n=28)	0%	0%	7%	11%	21%	36%	25%
EORTC Reference Value: Stage I & II	0%	1%	6%	16%	28%	31%	20%
Respondents: Stage III & IV (n=44)	2%	2%	11%	11%	27%	25%	20%
EORTC Reference Value: Stage III & IV	2%	2%	6%	18%	30%	26%	18%
Respondents: All patients (n=72)	1%	1%	10%	11%	25%	29%	22%
EORTC Reference Value: All Stages	2%	2%	8%	17%	28%	27%	16%

Table 4. Top 10 aspects mentioned most often by patients and carers as important in patients' HRQoL

Patients (n=72)				Carers (n=17)
Stage I (n=18)	**Stage II (n=10)**	**Stage III (n=16)**	**Stage IV (n=28)**	
Family*	Family*	Family*	Family*	Capability*
Good care*	Fear*	Worry*	Good medicines*	No AEs*
Finances†	Enjoy life	Normal life	Normal life*	Pain free*
Normal life†	Capability†	Therapy burden	Capability†	Drug effectiveness†
Support†	Good doctors†	Counselling†	Enjoy life†	Family†
Enjoy Life†	Good health†	Enjoy life†	Support†	Normal life†
Access to medicines‡	Normal life†	Good care‡	Good care	Access to medicines‡
Fear‡	Pain free†	Good doctors‡	Good health‡	Cure‡
Good doctors‡	Relapse†	Not to worry‡	Good information‡	Finances‡
Capability∓	Worry†	Pain free‡	Access to medicines∓	Good care‡
Friends∓			Friends∓	Good health‡
Good health∓			Pain free∓	Uncertainty‡
No anxiety∓				
Patient network∓				
Positive mood∓				
Work∓				

* The same number of respondents reported this aspect to be important in their HRQoL;
† The same number of respondents reported this aspect to be important in their HRQoL;
‡ The same number of respondents reported this aspect to be important in their HRQoL;
∓ The same number of respondents reported this aspect to be important in their HRQoL

As part of the survey, respondents were asked to rate the relevance of the questions originating from the EORTC QLQ-C30 to their or the patients' HRQoL (see Appendix 2). It can be seen that in our study sample patients with a different disease stage rated different questions as relevant to their HRQoL, and that carers also seemed to rate the relevance of questions differently than patients. For example, the question in the EORTC QLQ-C30 regarding 'Trouble doing strenuous activities' did not seem to be relevant (at all) or did not apply to the majority of patients with stage I and II melanoma, while approximately 50% of stage III and IV melanoma patients found this a relevant question. Another example showed that the question 'Have you had pain?' was rated as not relevant or does not apply to the majority of stage II melanoma patients, while more than 50% of stage III melanoma patients rated this question as (very) relevant. Also 60% of carers rated this question as (very) relevant.

Table 5. Examples to illustrate the extent to which questions from melanoma-specific HRQoL questionnaires correlate to aspects identified by patients and carers as important to their HRQoL, based on content analysis of survey responses

Questionnaire	Question	Relevance to patient population	Difference in wording	Example of patient response
EORTC QLQ-MEL38	Have you felt able to carry on with things as normal?	Relevant	Wording similar	'Wish to continue life as before.' 'Ability to life my life as normal as possible.'
EORTC QLQ-MEL38	Have you felt confident that a psychological support service would be available if you needed it?	Relevant	Wording similar	'Care and mental support (professionals and personal network).' 'Piece of mind that help is just at the end of a phone.'
EORTC QLQ-MEL38	Have you received realistic and reliable information about the extent (spread) of your disease?	Relevant	Wording may differ	'More facts and less fantasy. I could need statistics and knowledge.' 'Not being treated like a passive idiotic patient but being informed according to my intellectual and emotional needs.'
EORTC QLQ-MEL38	Have you had problem with pain at or near your melanoma site?	Relevant	Wording may differ	'Worry and fears about future pain and mortality.' 'Being able to live without pains.'

Table 5. Continued

Questionnaire	Question	Relevance to patient population	Difference in wording	Example of patient response
EORTC QLQ-MEL38	Have you been given enough time to think about the treatment options available to you?	Less relevant	Wording may differ	'Having treatment options explained and discussed with me.' 'Up to date knowledge of available treatments.'
EORTC QLQ-MEL38	Have you had swelling near your melanoma site?	Less relevant	NA	NA
EORTC QLQ-MEL38	Have you felt able to accept that melanoma is a serious condition?	Less relevant	Wording may differ	'Understanding how hard it is to live with cancer (friends, relatives and work).' 'Doctors who don't take your worries seriously.'
FACT-M	I get emotional support from my family	Relevant	Wording similar	'Being surrounded by people who support you through every step of the treatment.' 'Family and friends support.'
FACT-M	I worry that my condition will get worse	Relevant	Wording similar	'Worry every time it I have to go for my liver scan.' 'To be free from the constant worry and stress about mets.'
FACT-M	I have a lack of energy	Relevant	Wording may differ	'Have the energy to play with my children not be impatient because of fatigue.' 'Being able to exercise fully.'
FACT-M	I am bothered by side effects of treatment	Relevant	Wording may differ	'I'm very anxious about potential side-effects from treatment.' 'Being able to control drug side-effects.'
FACT-M	I have good range of movement in my arm or leg	Less relevant	NA	NA

NA, Not Applicable (e.g. respondents did not discuss anything regarding this question)

Table 5 provides a few examples to illustrate the extent to which current melanoma-specific HRQoL questionnaires (the EORTC QLQ-MEL38 and FACT-M) correlate to what patients indicate to be of influence to their HRQoL. Based on the aspects identified in the content analysis we determined whether a question in current melanoma-specific HRQoL questionnaires was relevant to our patient population. Additionally we assessed whether wording used in these questionnaires was similar to how patients describe this aspect in the survey. Some questions in the EORTC QLQ-MEL38 and FACT-M were relevant to our study population, while other questions seemed less relevant. For example, one question in the EORTC QLQ-MEL38 focused on patients being given enough time to think about the treatment options available. However, patients seemed to be more interested in discussing access to adequate and clear information on treatment options. Additionally, wording of questions posed in HRQoL questionnaires may differ from how patients interpret these questions. For example, questions regarding pain at the melanoma site, surgical site or headaches posed in the HRQoL questionnaires seemed to be aspects of pain that our study population did not focus on. Instead, respondents discussed pain in more general terms (e.g. future pains or experiencing pain). Additionally, while 14 of the 89 respondents discussed pain, 33 respondents focused more on being pain free as important for their HRQoL.

Discussion

In this study, the feasibility of using social media as a means to collect patient and carer perspectives on HRQoL was explored. Within the 30 days during which the survey was posted 89 full responses were received, showing the potential of using social media as a recruitment method. The majority of respondents accessed the survey via Facebook. Respondents resembled the general melanoma population in some aspects (e.g. melanoma stage distribution, overall HRQoL) but not others (e.g. gender distribution, educational level, geographic spread). Patients with different stages of melanoma and carers rated the relevance of questions posed in the EORTC QLQ-C30 differently. Qualitative analysis showed that some questions from the melanoma-specific EORTC QLQ-MEL38 and FACT-M questionnaires were relevant and others less relevant to our study population. Also, wording used in these questionnaires were sometimes different from how patients discussed these aspects.

Social media has been shown to provide a cost-saving and time-efficient manner to assemble valuable data.[22,36,37] Additionally, responses from audiences not usually included in randomised controlled clinical trials (RCTs) (e.g. women or patients with early stages of melanoma) can be collected.[38,39] The geographic spread of patients reached through social media is considerable, ranging in this study from the United States of America (U.S.A.), to Norway, Serbia and Romania. Moreover, data collection through social media allows patients the option to provide information at their own pace and within a trusted environment of their own choice. On the other hand, not all patients will have access to the internet,[36,40] the population of patients using the internet may not reflect all patients,[16,18,20-22] information bias may occur (e.g. duplication of social media messages or multiple messages from the same patient),[16-19] interpreting messages posted by patients may prove to be difficult for researchers, and it may be difficult to validate the authenticity of respondents via social media.[16] Keeping these disadvantages in mind, it should be emphasized that data collected through social media should be used complementary to traditional methods or provide insights where no data is otherwise available. The advantages of social media use may help increase the impact of HRQoL on REA of drugs by: increasing availability of HRQoL data for HTA, widening the scope of information from a broader patient group and increasing candidness of responses collected.

Findings from this study illustrated a difference between what patients and carers may regard as important aspects for HRQoL. Similar findings have been reported in previous research exploring responses of patients and carers to validated HRQoL questionnaires.[41] Despite the efforts invested by stakeholders to develop HRQoL questionnaires, it can thus be argued that they may not be equally implementable across patients and carers. Moreover, differences on important aspects of HRQoL extended to patients' disease stage. Comparable findings in previous research have enticed discussions for the development of individualised HRQoL questionnaires.[13,42,43] This raises the question of which form of HRQoL questionnaires HTA agencies should resort to within REA's. Moreover, it raises doubts as to whether current questionnaires are sufficient to distinguish between HRQoL of patients with different stages of melanoma. In fact, the incremental value of cancer- or melanoma-specific questionnaires for REA's may be questionable when compared to more general tools such as the EQ-5D, considering the fact that even they may be unable to distinguish between the HRQoL of patients with different disease stages. Provided that innovative, expensive drugs are targeted at stage III/IV patients (i.e. metastatic melanoma), as well as the marginal relative incremental gains in overall survival amongst innovative drugs and toxicity profiles

associated with their use, it may therefore become necessary to develop separate stage-specific HRQoL questionnaires for patients and carers to better delineate HRQoL gains with new treatments in the future.[44,45]

Meanwhile, findings on the varying relevance of questions posed in available cancer-specific or melanoma-specific questionnaires to patients may provide insights as to why completion rates for HRQoL questionnaires remain low, whether in the setting of RCTs or routine practice.[5,46] Controversy regarding the relevance of questions posed in HRQoL in comparison to patient needs has been repeatedly cited in literature on several disease areas.[13,14,47] A possible explanation for this phenomenon may be that HRQoL questionnaires are conventionally developed with a physician- or scientific focus whereby the emphasis is set on aspects such as reliability, validity, and cross-cultural relevance, rather than a patient-centred approach which elicits thorough patient input at all stages of development.[13,14,48] The subsequent irrelevance of certain questions, in combination with factors such as disease burden and practical difficulties associated with completing paper-based questionnaires, may result in patients feeling less inclined to provide responses. Consequently, a paucity of HRQoL data for purposes such as REA ensues. If developers of new HRQoL questionnaires would address abovementioned limitations of current ones, it may thus be worthwhile to use insights provided by patients and carers through social media to ensure that the newly developed questionnaires are deemed relevant to their personal perspectives, thereby encouraging them to complete such questionnaires.

Strengths

This study has several strengths. First, three different social media channels were used to distribute the survey, representing two different forms of social media: Twitter (micro-blogs), Facebook and LinkedIn (social networking sites). Second, open-ended questions were used in the survey, allowing respondents the opportunity to express which aspects were of influence to their HRQoL in their own terms and length. This ensured that responses compiled were likely to represent the views of their writers accurately and comprehensively. Third, two researchers conducted inductive content analysis, independently, on free text to assess the survey responses. This approach avoids limitations associated with computerised approaches such as missing misspelled words or misinterpreting slang and sarcasm. Moreover, all discrepancies related to the analysis were resolved by consensus amongst both researchers to ensure validity. Fourth, responses by patients were stratified by disease stage to highlight any potential differences in what patients may deem relevant to HRQoL per stage. Due to the

low number of survey respondents, results are merely indicative of differences and inform hypotheses generation for future research.

Limitations

A few limitations can be identified in this study. First, the survey was developed and written in English. This was not the native language of a considerable number of the respondents in this study, which may have impacted their ability to adequately represent their thoughts on the issues raised. Additionally, this may have led to selection bias since 50% of respondents were English-speaking. Second, this study provided a cross-sectional analysis of melanoma patient perspectives on HRQoL. Although this information is valuable in the context of this feasibility study, HTA decision-making on the effectiveness of melanoma drugs in practice conventionally requires longitudinal data collection on HRQoL. Therefore, the current study does not shed light on potential attrition rates in questionnaire completion or the robustness of findings from longitudinal data collection through social media. Third, the comparison of patient and carers´ perspectives on HRQoL was performed against three validated cancer- and melanoma-specific questionnaires. Other generic HRQoL instruments exist which were not included, such as the SF-36 and EQ-5D questionnaires. Provided the relevance of such generic measures for REA of drugs, this may impact the relevance of findings for HTA. On the other hand, it may be argued that the relevance of such generic measures for the comparison made would have been predictably lower than for the selected disease-specific instruments.

Conclusion

Social media may provide a valuable tool to assess patient and carer perspectives on HRQoL, thus potentially increasing the availability and impact of HRQoL data in REA of drugs. However insights gleaned through social media are not easily generalizable to the broader melanoma patient population. Differences emerge between what patients of varying melanoma stages and carers consider important for HRQoL. Cancer- and melanoma- specific HRQoL questionnaires currently available do not seem to correlate fully with what patients view as important in HRQoL, particularly in relation to wording of issues. This raises the question of how information generated from current cancer- and melanoma-specific HRQoL questionnaires could be used for HTA decision-making and whether new, patient-centred, stage-specific instruments should be developed that better reflect patient perspectives on HRQoL.

Furthermore, current knowledge on the potential approaches for using social media to inform HTA decision-making is sparse. Although this study sheds light on the potential use of social media as a medium for gathering cross-sectional data on melanoma patient perspectives on HRQoL through questionnaires, future research should also aim to address the wide array of other potential uses, such as: the use of social media to collect longitudinal data on HRQoL, the use of data-mining approaches to glean insights on HRQoL from other channels (e.g. patient forums) and the methods for combining the potential value of the two different approaches for the use of social media (i.e. as a medium vs. data mining) for HTA decision-making. Additionally, since this was a feasibility study, a similar study on larger scale would allow for robust quantitative analysis of aspects that are important to the HRQoL of melanoma patients.

Authorship Statement

RK and AM designed the study in collaboration with the co-authors. RK designed the survey and analysed the data together with author AM. RK wrote the draft method and results section, and author AM wrote the draft introduction and discussion section. All co-authors actively contributed throughout the conduct of the study and critically reviewed and approved the manuscript.

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Appendices

Appendix 1. The Melanoma Quality of Life Survey: a 25-item web-based survey

Dear Melanoma patient or carer,

What is Quality of Life in Melanoma for YOU?

This study is part of the GetReal project and is conducted as collaboration between MPNE, the Melanoma Patient Network Europe, and ZIN, the Dutch National Healthcare Institute. So far, few studies have looked at what Melanoma patients themselves consider important for their own Quality of Life. The aim of this study is therefore to find out what truly matters to the Melanoma patients reached through our network. Quality of Life data is also increasingly used for the approval and reimbursement of new therapies – so please take the time to share your thoughts! We would like to understand the influence of the Melanoma stage, the time of diagnosis, the country you live in and Melanoma therapies on the Quality of Life of Melanoma patients. We also want to see if social media could be used to collect such information on patient perspectives. More information about this collaboration can be found on our website.

This survey should take 20 minutes to complete. Your answers are confidential and we will only publish anonymous results. Insights and reports will obviously be shared via the Melanoma Patient Network Europe channels!

Thank you for you time and effort.

MPNE and ZIN

Melanoma Patient Network Europe and National Healthcare Institute

We value your opinion

1. Quality of Life in Melanoma – which aspects come to your mind?

1. [Open Field]
2. [Open Field]
3. [Open Field]
4. [Open Field]
5. [Open Field]
6. [Open Field]
7. [Open Field]
8. [Open Field]
9. [Open Field]
10. [Open Field]

2. What is Quality of Life in Melanoma for you?

[Open Field]

3. On a scale from 1 to 7, please rate your/the patient's Quality of Life today

	1 – poor	2	3	4	5	6	7 – Excellent
Quality of Life	O	O	O	O	O	O	O

4. The 3 things that today make your/ the Melanoma patient's Quality of Life good

1. [Open Field]
2. [Open Field]
3. [Open Field]

5. The 3 things that today make your/ the Melanoma patient's Quality of Life good

1. [Open Field]
2. [Open Field]
3. [Open Field]

6. The single thing that would improve your/ the Melanoma patient's Quality of Life right now?

[Open Field]

7. How important are for you

	Not important at all	Not important	Neutral	Important	Very important
Physical well-being (e.g. energy level, nauseau, pain)	O	O	O	O	O
Social/ Family well-being (e.g. support from family and friends, sex life)	O	O	O	O	O
Emotional well-being (e.g. feeling sad or nervous, worries related to Melanoma or treatments)	O	O	O	O	O
Functional well-being (e.g. ability to work, sleep and enjoy life)	O	O	O	O	O
Other (please specify below)	O	O	O	O	O
Other (please specify)	[Open Field]				

8. Please comment on question 7

[Open Field]

9. How relevant are the following aspects for you

	Not relevant at all	Not relevant	Neutral	Relevant	Very relevant	Does not apply to me
Trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase	O	O	O	O	O	O
Trouble taking a long walk	O	O	O	O	O	O
Trouble taking a short walk outside of the house	O	O	O	O	O	O
Need to stay in bed or a chair during the day	O	O	O	O	O	O
Need help with eating, dressing, washing yourself or using the toilet	O	O	O	O	O	O
Limitations in doing either your work or other daily activities	O	O	O	O	O	O
Short of breath	O	O	O	O	O	O
Pain	O	O	O	O	O	O
Needed more time to rest	O	O	O	O	O	O
Trouble sleeping	O	O	O	O	O	O
Feeling weak	O	O	O	O	O	O
Lack of appetite	O	O	O	O	O	O
Nausea/ Feeling sick	O	O	O	O	O	O
Have you vomited?	O	O	O	O	O	O
Were you constipated?	O	O	O	O	O	O
Diarrhoea	O	O	O	O	O	O
Tiredness	O	O	O	O	O	O
Did pain interfere with your daily activities?	O	O	O	O	O	O
Difficulty in concentrating on things, like reading a newspaper or watching television	O	O	O	O	O	O
Feeling tense	O	O	O	O	O	O
Worrying	O	O	O	O	O	O

Feeling irritable	O	O	O	O	O	O
Feeling depressed	O	O	O	O	O	O
Difficulty remembering things	O	O	O	O	O	O
Physical condition or medical treatment interfered with your family life	O	O	O	O	O	O
Physical condition or medical treatment interfered with your social activities	O	O	O	O	O	O
Physcial condition or medical treatment caused you financial difficulties	O	O	O	O	O	O
Other (please specify)	[Open Field]					

10. Please comment on question 8

[Open Field]

Tell us about yourself

11. I am

O Female

O Male

12. What is your Country of Residence?

13. What is your age?

14. What is the highest level of education you have completed?

15. Where did you find this survey?

16. Your relationship to Melanoma

	Stage I	Stage II	Stage III	Stage IV	N/A
I am a Melanoma patient	O	O	O	O	O
I am the carer or a Melanoma patient whose disease is in	O	O	O	O	O

Other (please specify) [Open Field]

17. The Melanoma diagnosis was

18. What type of Melanoma do you or the patient have?

Other (please specify) [Open Field]

19. Which mutations does your/ the patient's Melanoma have?

O BRAF mutant
O BRAF wild-type
O NRAS mutant
O c-kit mutant
O GNAQ/ GNA11
O I don't know
O Other (please specify)
[Open Field]

Melanoma therapies and treatments

20. Did you have surgery for your Melanoma?

O No

O Yes

If yes, what type of surgery?

[Open Field]

21. Did/ do you have radiotherapy for your Melanoma?

O No
O Yes

If yes, what type of radiotherapy?

[Open Field]

22. Did/ do you have chemotherapy for your Melanoma?

No

Yes

If yes, what type of chemotherapy?

[Open Field]

23. Did/ do you have immune therapies for your Melanoma? (please tick all that apply)

O No
O Ipilimumab/ YERVOY® - BMS
O Pembrolizumab/ KEYTRUDA® - MSD
O Nivolumab/ OPDIVO® - BMS
O T-Veck/ Talimogene Laherparepvec/ IMLYGIC® - Amgen
O Pidilizumab (CT011 anti-PD1) – Curetech
O Atezolizumab (anti-PD-L1) – BMS
O BMS936559 (anti-PDL1) – BMS
O Dendritic Cell Vaccine – academic
O Adaptive Cell Therapies like TILs (T-infiltrating Lymphocytes) – academic
O Other (please specify)
[Open Field]

24. Did/ do you have targeted therapies for your Melanoma? (please tick all that apply)

O No
O Vemurafenib/ ZELBORAF® - Roche
O Dabrafenib/ TAFINLAR® - Ex-GSK, now Novartis
O Trametinib/ MEKINIST® - Ex-GSK, now Novartis
O Cobimetinib/ COTELLIC® - Roche
O Encorafenib/ LGX8181 – Ex-Novartis, now Array
O Binimetinib MEK 162 – Ex-Novartis, now Array
O Other (please specify)
[Open Field]

Thank you

25. Anything else you would like to let us know?
[Open Field]

Thank you for helping us understand what Quality of Life means to Melanoma patients.
The results of this survey will be shared in any anonymous form with the MPNE network and the general public. To make sure you don't miss updates, please sign up to the MPNE newsletter.
MPNE and ZIN

Appendix 2. Relevance of questions from EORTC QLQ-C30 questionnaire in our study population, for each question in the EORTC QLQ-C30 questionnaire the percentages are calculated per stage

Question in EORTC QLQ-C30	Stage	Relevance					
		Not relevant at all	Not relevant	Neutral	Relevant	Very relevant	Does not apply to me
Trouble doing strenuous activities	Stage I (n=17)	18%	24%	6%	12%	12%	29%
	Stage II (n=10)	40%	10%	20%	-	-	30%
	Stage III (n=16)	19%	12%	-	25%	31%	12%
	Stage IV (n=28)	18%	7%	18%	29%	18%	11%
	Carers (n=19)	11%	5%	21%	11%	32%	21%
Trouble taking a long walk	Stage I (n=17)	12%	24%	6%	6%	24%	29%
	Stage II (n=10)	40%	30%	-	-	-	30%
	Stage III (n=16)	19%	6%	12%	6%	38%	19%
	Stage IV (n=28)	18%	7%	18%	29%	18%	11%
	Carers (n=19)	5%	5%	21%	21%	21%	26%
Trouble taking a short walk outside the house	Stage I (n=18)	28%	22%	-	-	17%	33%
	Stage II (n=10)	40%	20%	-	-	10%	30%
	Stage III (n=16)	25%	19%	6%	19%	12%	19%
	Stage IV (n=28)	18%	25%	14%	14%	7%	21%
	Carers (n=19)	17%	17%	-	17%	22%	28%
Need to stay in bed or a chair during the day	Stage I (n=17)	18%	24%	12%	6%	-	41%
	Stage II (n=10)	50%	10%	-	10%	-	30%
	Stage III (n=16)	25%	12%	6%	31%	6%	19%
	Stage IV (n=28)	25%	21%	11%	14%	11%	18%
	Carers (n=19)	11%	21%	11%	11%	21%	26%
Need help with eating, dressing, washing yourself or using the toilet	Stage I (n=17)	18%	18%	12%	-	6%	47%
	Stage II (n=10)	70%	-	-	-	-	30%
	Stage III (n=16)	44%	6%	-	25%	-	25%
	Stage IV (n=28)	50%	7%	4%	4%	7%	29%
	Carers (n=19)	26%	16%	-	11%	21%	26%
Limitations in doing either your work or other daily activities	Stage I (n=17)	18%	18%	6%	18%	18%	24%
	Stage II (n=10)	60%	-	-	10%	-	30%
	Stage III (n=16)	19%	6%	12%	31%	25%	6%
	Stage IV (n=28)	18%	7%	7%	25%	32%	11%
	Carers (n=19)	11%	-	26%	21%	26%	16%
Limitations in pursuing your hobbies or other leisure time activities	Stage I (n=17)	6%	12%	12%	18%	35%	18%
	Stage II (n=10)	50%	10%	10%	10%	-	20%
	Stage III (n=15)	13%	7%	-	53%	7%	20%
	Stage IV (n=27)	15%	7%	7%	33%	26%	11%
	Carers (n=19)	5%	5%	11%	32%	26%	21%

Appendix 2. Continued

Question in EORTC QLQ-C30	Stage	Relevance					
		Not relevant at all	Not relevant	Neutral	Relevant	Very relevant	Does not apply to me
Short of breath	Stage I (n=17)	18%	29%	-	6%	12%	35%
	Stage II (n=10)	40%	10%	10%	-	-	40%
	Stage III (n=16)	31%	6%	12%	12%	19%	19%
	Stage IV (n=28)	43%	4%	-	29%	7%	18%
	Carers (n=19)	22%	11%	11%	-	22%	33%
Pain	Stage I (n=16)	12%	12%	12%	19%	6%	38%
	Stage II (n=10)	50%	10%	-	10%	-	30%
	Stage III (n=16)	25%	6%	6%	38%	19%	6%
	Stage IV (n=28)	36%	4%	11%	21%	11%	18%
	Carers (n=19)	17%	-	11%	11%	50%	11%
Needed more time to rest	Stage I (n=16)	6%	19%	12%	12%	25%	25%
	Stage II (n=10)	20%	10%	10%	20%	10%	30%
	Stage III (n=15)	7%	7%	7%	53%	20%	7%
	Stage IV (n=28)	21%	4%	7%	29%	32%	7%
	Carers (n=19)	16%	16%	5%	26%	21%	16%
Trouble sleeping	Stage I (n=17)	6%	6%	24%	18%	18%	29%
	Stage II (n=10)	20%	10%	-	30%	10%	30%
	Stage III (n=16)	12%	12%	25%	38%	12%	-
	Stage IV (n=28)	21%	-	7%	25%	36%	11%
	Carers (n=19)	-	5%	11%	32%	32%	21%
Feeling weak	Stage I (n=16)	6%	19%	25%	19%	-	31%
	Stage II (n=10)	40%	10%	10%	10%	-	30%
	Stage III (n=16)	12%	6%	19%	44%	12%	6%
	Stage IV (n=27)	37%	7%	7%	15%	22%	11%
	Carers (n=19)	11%	5%	5%	26%	37%	16%
Lack of appetite	Stage I (n=17)	18%	29%	18%	-	-	35%
	Stage II (n=10)	50%	-	20%	-	-	30%
	Stage III (n=16)	25%	19%	6%	19%	12%	19%
	Stage IV (n=27)	33%	7%	15%	19%	4%	22%
	Carers (n=19)	26%	5%	11%	11%	21%	26%
Nausea/ Feeling sick	Stage I (n=17)	24%	18%	6%	6%	-	47%
	Stage II (n=10)	60%	-	-	10%	-	30%
	Stage III (n=16)	25%	19%	6%	6%	25%	19%
	Stage IV (n=28)	32%	11%	7%	11%	11%	29%
	Carers (n=19)	21%	26%	5%	11%	16%	21%
Have you vomited?	Stage I (n=17)	29%	18%	-	-	-	53%
	Stage II (n=10)	70%	-	-	-	-	30%
	Stage III (n=16)	50%	-	-	19%	6%	25%
	Stage IV (n=28)	43%	7%	11%	7%	7%	25%
	Carers (n=19)	26%	21%	11%	5%	-	37%

Appendix 2. Continued

Question in EORTC QLQ-C30	Stage	Relevance					
		Not relevant at all	Not relevant	Neutral	Relevant	Very relevant	Does not apply to me
Were you constipated?	Stage I (n=16)	19%	19%	6%	6%	-	50%
	Stage II (n=10)	60%	10%	-	-	-	30%
	Stage III (n=16)	38%	6%	6%	25%	6%	19%
	Stage IV (n=28)	29%	4%	11%	18%	11%	29%
	Carers (n=19)	11%	5%	26%	16%	-	42%
Diarrhea	Stage I (n=16)	19%	19%	12%	-	-	50%
	Stage II (n=10)	70%	-	-	-	-	30%
	Stage III (n=16)	38%	6%	6%	25%	6%	19%
	Stage IV (n=28)	32%	11%	11%	18%	14%	14%
	Carers (n=19)	16%	26%	5%	21%	5%	26%
Tiredness	Stage I (n=16)	12%	6%	-	50%	12%	19%
	Stage II (n=10)	20%	-	-	50%	10%	20%
	Stage III (n=16)	12%	-	12%	38%	25%	12%
	Stage IV (n=28)	18%	-	7%	21%	54%	-
	Carers (n=19)	11%	-	-	32%	42%	16%
Did pain interfere with your daily activities?	Stage I (n=17)	18%	12%	-	29%	6%	35%
	Stage II (n=10)	30%	20%	-	20%	-	30%
	Stage III (n=16)	25%	6%	12%	25%	12%	19%
	Stage IV (n=28)	36%	7%	11%	7%	21%	18%
	Carers (n=19)	11%	11%	11%	16%	21%	32%
Difficulty in concentrating on things	Stage I (n=17)	18%	6%	29%	18%	12%	29%
	Stage II (n=9)	22%	-	11%	22%	22%	22%
	Stage III (n=15)	33%	-	13%	33%	20%	13%
	Stage IV (n=28)	11%	7%	18%	11%	32%	7%
	Carers (n=19)	5%	26%	5%	26%	11%	26%
Feeling tense	Stage I (n=17)	6%	6%	12%	35%	29%	12%
	Stage II (n=10)	10%	10%	-	30%	30%	20%
	Stage III (n=16)	12%	-	25%	25%	25%	12%
	Stage IV (n=28)	11%	4%	18%	29%	36%	4%
	Carers (n=19)	-	11%	5%	26%	47%	11%
Worrying	Stage I (n=17)	-	-	12%	35%	41%	12%
	Stage II (n=10)	-	10%	-	30%	40%	20%
	Stage III (n=16)	-	6%	-	31%	44%	19%
	Stage IV (n=28)	7%	11%	11%	32%	32%	7%
	Carers (n=19)	5%	16%	-	16%	47%	16%
Feeling irritable	Stage I (n=16)	-	6%	19%	38%	25%	12%
	Stage II (n=10)	10%	10%	20%	10%	20%	30%
	Stage III (n=14)	-	21%	29%	29%	14%	7%
	Stage IV (n=28)	11%	7%	11%	50%	18%	4%
	Carers (n=19)	-	16%	11%	37%	21%	16%

Appendix 2. Continued

Question in EORTC QLQ-C30	Stage	Relevance					
		Not relevant at all	**Not relevant**	**Neutral**	**Relevant**	**Very relevant**	**Does not apply to me**
Feeling depressed	Stage I (n=17)	-	6%	12%	35%	18%	29%
	Stage II (n=10)	10%	-	20%	20%	30%	20%
	Stage III (n=16)	-	12%	25%	19%	38%	6%
	Stage IV (n=28)	4%	18%	21%	18%	21%	18%
	Carers (n=19)	5%	16%	5%	12%	42%	11%
Difficulty remembering things	Stage I (n=15)	7%	-	27%	33%	7%	27%
	Stage II (n=10)	10%	20%	-	10%	30%	30%
	Stage III (n=16)	19%	19%	19%	19%	12%	12%
	Stage IV (n=27)	19%	7%	19%	19%	22%	15%
	Carers (n=19)	11%	21%	11%	21%	16%	21%
Physical condition or medical treatment interfered with your family life	Stage I (n=16)	6%	6%	6%	19%	25%	38%
	Stage II (n=10)	20%	-	20%	20%	20%	20%
	Stage III (n=16)	12%	-	25%	25%	25%	12%
	Stage IV (n=28)	7%	-	21%	32%	32%	7%
	Carers (n=19)	5%	5%	5%	32%	32%	21%
Physical condition or medical treatment interfered with your social activities	Stage I (n=16)	6%	6%	6%	25%	31%	25%
	Stage II (n=10)	20%	-	-	30%	20%	30%
	Stage III (n=16)	12%	-	12%	31%	31%	12%
	Stage IV (n=28)	4%	-	18%	29%	36%	14%
	Carers (n=19)	5%	5%	5%	32%	32%	21%
Physical condition or medical treatment caused you financial difficulties	Stage I (n=18)	12%	12%	-	24%	18%	35%
	Stage II (n=10)	30%	-	10%	20%	20%	20%
	Stage III (n=16)	19%	12%	12%	19%	19%	19%
	Stage IV (n=28)	11%	7%	25%	25%	18%	14%
	Carers (n=19)	11%	16%	-	11%	42%	21%

Chapter 6

Information Patients With Melanoma Spontaneously Report About Health-Related Quality of Life on Web-Based Forums: Case Study

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Abstract

Background: There is a general agreement on the importance of health-related quality of life (HRQoL). This type of information is becoming increasingly important for the value assessment of health technology assessment agencies in evaluating the benefits of new health technologies, including medicines. However, HRQoL data are often limited, and additional sources that provide this type of information may be helpful.

Objective: We aim to identify the HRQoL topics important to melanoma patients based on web-based discussions on public social media forums.

Methods: We identified 3 public web-based forums from the United States and the United Kingdom, namely the Melanoma Patient Information Page, the Melanoma International Forum, and MacMillan. Their posts were randomly selected and coded using qualitative methods until saturation was reached.

Results: Of the posts assessed, 36.7% (150/409) of posts on Melanoma International Forum, 45.1% (198/439) on MacMillan, and 35.4% (128/362) on Melanoma Patient Information Page focused on HRQoL. The 2 themes most frequently mentioned were *mental health* and *(un)certainty*. The themes were constructed based on underlying and more detailed codes. Codes related to *fear, worry and anxiety*, *uncertainty*, and *unfavorable effects* were the most-often discussed ones.

Conclusions: Web-based forums are a valuable source for identifying relevant HRQoL aspects in patients with a given disease. These aspects could be cross-referenced with existing tools and they might improve the content validity of patient-reported outcome measures, including HRQoL questionnaires. In addition, web-based forums may provide health technology assessment agencies with a more holistic understanding of the external aspects affecting patient HRQoL. These aspects might support the value assessment of new health technologies and could therefore help inform topic prioritization as well as the scoping phase before any value assessment.

Introduction

Background

Decisions on the reimbursement of innovative medicines in Europe are most prominently based on the recommendations of national health technology assessment (HTA) agencies. Conventionally, these HTA recommendations are prepared directly after market-authorization of medicines. The starting point for these HTAs is the assessment of (added) therapeutic value, also known as relative effectiveness assessment, and subsequently, cost-effectiveness assessments. In both, relative effectiveness assessments and cost-effectiveness assessments, outcome measures such as the overall survival rate, adverse events (AEs), and health-related quality of life (HRQoL) are considered.

From the perspective of patients, HRQoL is an important outcome measure because it can capture how disease and treatment affect a patient's quality of life.[1] This is especially of interest in diseases such as cancer, where medicines may increase overall survival rates but may cause considerable toxicity. Therefore, HRQoL intends to inform HTA agencies on the relevance and added value of new oncology treatments for patients, for instance, if the medicine improves HRQoL by halting the progression of the disease, or alternatively, decreases HRQoL if toxicity or AEs have a large impact on the patient's well-being.

Although the assessment of HRQoL is becoming increasingly important in different areas of healthcare, relevant HRQoL data are often unavailable. For instance, patients with severe disease seem less likely to complete HRQoL questionnaires compared with their healthier counterparts.[2,3] The use of complicated HRQoL instruments increases respondent burden and may also lead to lower completion rates. Furthermore, patients might not be motivated to complete HRQoL questionnaires in a research setting if tangible respondent benefits are not delivered. Overall, HRQoL data are currently only sparsely represented in HTA reports for oncological products. More specifically, only in a third of HTA assessments were HRQoL data used,[4] leading to a low impact of HRQoL on HTA decision-making despite the general recognition of the importance of HRQoL for patients and society.

In addition to the limited availability of HRQoL data, current methods used to measure HRQoL may fail to truly capture what is most relevant to patients,[5] which may result in incorrect overall interpretation. Therefore, there is a continuous search for sources that provide additional relevant information

on HRQoL. Social media is a convenient and well-established communication source and therefore presents an obvious potential option. Patients often use social media to gather information on their health condition and treatment options, to share their experiences, and to find social support.[6-8] Previous research has also shown that social media may help identify HRQoL topics of importance to patients, prioritize the topics most relevant to patients, or help in the distribution of HRQoL questionnaires.[9-12] Melanoma is an area of oncology that has seen the rapid introduction of several classes of new therapeutics with new modes of action, increasing the likelihood of existing HRQoL tools failing to capture patient-relevant outcomes.[13-15] Concomitantly, several web-based patient forums for melanoma have been active.

Objectives

To evaluate the potential relevance of social media as a meaningful source of HRQoL information for HTA, we identified the HRQoL topics that are most important to melanoma patients based on discussions from web-based forums. Following the logic that in an unsupervised setting, patients would bring up topics relevant to them rather than being triggered by, for instance, a questionnaire, we focused on the research question: Which HRQoL topics do melanoma patients and their caregivers spontaneously discuss on the web?

Methods

Overview

For this study, we focused on public web-based forums that are publicly accessible to anyone, as opposed to private patient communities. These public web-based forums provide peer support for a range of medical conditions, allowing the patients to share their experiences and provide information.[16-18] In a previous study, we collected patient perspectives on HRQoL from private social media sources, including a private Facebook (Facebook, Inc) group for melanoma patients.[9] Using a different type of social media in this study allows for comparisons between the different sources of social media regarding the HRQoL topics discussed.

Selection of Web-Based Forums

The public web-based forums were identified using 2 internet search engines, namely (1) Google (Google, Inc) and (2) Bing (Microsoft, Inc), which are currently the most popular search engines in the world.[19,20] Searches were conducted in

English, with a combination of the search terms *melanoma*, *forum*, *message board*, and *discussion board*. Browser history was cleared before each search because the previous searches might influence the search findings. This forum search was conducted on 5 consecutive days starting June 4, 2019, to account for the websites being unavailable owing to maintenance issues. The search results from the first 2 pages shown by (1) Google and (2) Bing were extracted and assessed for eligibility, and any advertisements or images were excluded.

Forums were eligible for inclusion based on the following 3 criteria: (1) the website had been active for ≥5 years based on the publication dates of posts, (2) at least 2000 posts had been posted on the forum, and (3) ≥5 new posts had been posted in the past week. We identified 3 forums as eligible for inclusion: Melanoma Patients Information Page (MPIP), Melanoma International Forum (MIF), and MacMillan Cancer Support Online Community for Melanoma Patients. Each forum was informed of our intention to use their publicly available posts for research purposes via email. Both MPIP and MIF are forums based in the United States and MacMillan is based in the United Kingdom. MPIP and MIF focus solely on melanoma patients, whereas MacMillan provides information to support cancer patients in general, in addition to having 64 cancer-specific forums (e.g. melanoma, Hodgkin lymphoma, pancreatic cancer, and unknown primary cancer).[21-23]

Data Extraction

No login was used to gain access to any of the posts extracted, nor was login required on any of the forums. Each forum thread was sorted by the date of the last post, after which all the threads were collected. A thread is defined as a collection of posts, with an initial post that introduces a specific topic and the subsequent replies posted by one or more members of the forum. We collected the complete threads from each forum using the R package *rvest* (R Core Team) in September 2019.[24] We collected the following data: title of the thread, text from each post, username of each post, date and time of each post, and whether a post was the original post or a reply. Each username was given a user ID to ensure anonymity.

Data Analysis

We coded the posts using the coding scheme developed in our previous study,[9] in which members of the Melanoma Patient Network Europe, an established patient network for melanoma patients, caregivers, and advocates, were approached via its multiple social media channels to anonymously complete a 25-item web-based survey. In this survey, questions regarding sociodemographic

and clinical characteristics and several open questions exploring patient and caregiver perspectives on HRQoL (e.g. "What is HRQoL in melanoma for you?", "Name 3 things that deteriorate your/the melanoma patient's HRQoL today?") were posed. Two researchers independently performed inductive content analysis on the responses to the open-ended questions and assigned codes, and any discrepancies in coding were resolved by consensus. As these themes and codes may not have covered all the topics spontaneously discussed in the forums, we created new themes and codes as required. The following themes were added: *alone* and *coping*, and the code *guilt* was added to the theme *certainty*. In addition, we adjusted the coding scheme to be more concise.

We excluded the posts that did not focus on HRQoL or melanoma, provided advice or shared experience, asked a question or provided information, or offered support. We defined HRQoL as the patient's subjective perception of the impact of the disease and its treatment on the physical, psychological, and social aspects of daily life.[25,26] From each forum, a random sample of 100 posts was coded by 2 authors (RRJK, DMJD, WGG and MLB). Agreement regarding the inclusion and exclusion of posts between the coders was 74% for MPIP (RRJK and DMJD), 85% for MIF (RRJK and WGG), and 83% for MacMillan (RRJK and MLB); any disagreements were discussed and resolved by consensus. From this random sample, 44% (44/100) were included in this study from MPIP, 61% (61/100) from MIF, and 63% (63/100) from MacMillan. Subsequently, author RRJK continued coding the posts selected randomly from each forum until 100 posts which referred to HRQoL aspects were included. After this, the posts were coded in batches of 25 until saturation. We defined saturation as not being able to identify a new emerging theme in 2 consecutive batches of 25 posts.[27] Owing to the vast number of posts in each forum, we decided to code until saturation because this was sufficient to identify which HRQoL aspects were relevant to melanoma patients. When author RRJK was unsure about a specific post or code, the issue was discussed and resolved by consensus among authors (RRJK, DMJD, MLB, and WGG). A total of 72.4% (262/362) posts for MPIP, 75.6% (309/409) for MIF, and 77.2% (339/439) for MacMillan were assessed solely by author RRJK. Coder drift was not assessed in this study, and therefore, poses a potential coding bias.

Covering all the posts assessed, we conducted an analysis of the number of threads and reply posts by each unique user to assess how often the same person initiated a thread or replied to an initial post. As a subanalysis, we assessed the subforums available on MIF in more detail. MIF provides separate forums for melanoma patients with stage I and II, stage III and stage IV, as well as separate

forums for newly diagnosed (ND) stage I and II patients and ND stage III and IV patients. This allowed us to evaluate which HRQoL topics were important for melanoma patients at different disease stages. The results from analysing the forum posts have been described qualitatively. This study was conducted in accordance with the Standards for Reporting Qualitative Research.[28] All data were collected, coded, stored, and analysed using R version 3.4.4 (R Core Team) and NVIVO (QSR International, Inc) version 12.[29,30]

Results

Overview

A total of 14,755, 6798, and 1671 threads were collected from MPIP, MIF, and MacMillan, respectively. This resulted in 88,261, 23,911, and 9551 original posts from MPIP, MIF, and MacMillan, respectively. A total of 409 posts from 189 unique users were assessed from MIF, as were 439 posts from 359 unique users from MacMillan and 362 posts from 243 unique users from MPIP (Figure 1). After the exclusion of irrelevant posts, 150 posts from 112 unique users, 198 posts from 164 unique users, and 128 posts from 96 unique users were included in our assessment from MIF, MacMillan, and MPIP, respectively.

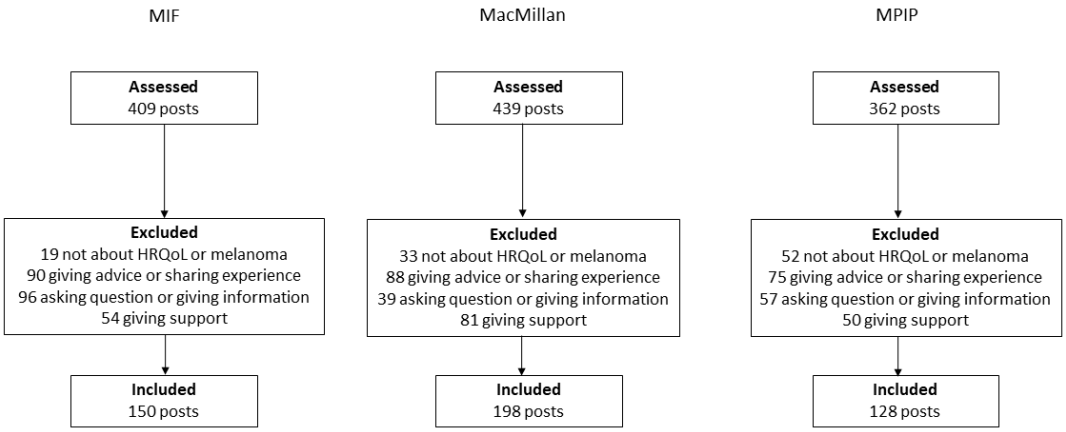

Figure. 1 Overview of in- and exclusion of forum posts

We determined how often the same user started a thread and posted a reply (See Appendix 3). Some users started 1 thread but did not reply to any other post (46/189, 24.3% on MIF; 130/359, 36.2% on MacMillan; and 71/243, 29.2% on MPIP). Another group of users posted 1 reply, but did not start any threads

(99/189, 52.4% MIF; 67/359, 18.7% MacMillan; and 52/243, 21.4% MPIP). Finally, a number of users started 1 thread and posted 1 reply (9/189, 4.8% MIF; 69/359, 19.2% MacMillan; and 32/243, 13.2% MPIP). Overall, 95.8% (181/189) of the users on MIF, 95% (341/359) on MacMillan, and 92.6% (225/243) on MPIP posted ≤5 posts (either as the initial thread or reply post). Only a few users in each forum contributed to a greater extent. Only 2 major outliers can be identified: 1 on MPIP, where 1 user started 45 threads and posted 26 replies, and 1 on MIF, where 1 user started 20 threads and posted 74 replies.

On all 3 forums, the 2 most-often identified themes were *mental health* and *certainty* (Table 1). More than half of the posts mentioned aspects related to *mental health* (85/150, 56.7% MIF; 126/198, 63.6% MacMillan; and 69/128, 53.9% MPIP), and at least a third of the posts mentioned information relevant to *certainty* (63/150, 42% MIF; 80/198, 40.4% MacMillan; and 40/128, 31.3% MPIP). Other often-mentioned themes were *healthcare communication* (32/150, 21.3%) and *unfavourable effects* (28/150, 18.7%) on MIF, *healthcare access* (43/198, 21.7%) and *unfavourable effects* (27/198, 13.6%) on MacMillan, and *healthcare access* (20/128, 15.6%) and *unfavourable effects* (21/128, 16.4%) on MPIP.

Table 1. Total number and percentage of posts mentioning a specific theme on each forum (N=476)

Theme	Total posts per forum, n (%)		
	MIF[a] (n=150)	MacMillan (n=198)	MPIP[b] (n=128)
Mental health	85 (56.7)	126 (63.6)	69 (53.9)
Certainty	63 (42.0)	80 (40.4)	40 (31.2)
Healthcare communication	32 (21.3)	21 (10.6)	12 (9.4)
Unfavourable effects	28 (18.7)	27 (13.6)	21 (16.4)
Healthcare access	16 (10.6)	43 (21.7)	20 (15.6)
Healthcare general	17 (11.3)	23 (11.6)	18 (14.1)
Disease status	16 (10.6)	5 (2.5)	9 (7.0)
Support	15 (10.0)	26 (13.1)	12 (9.4)
Coping	14 (9.3)	22 (11.1)	4 (3.1)
Social life	14 (9.3)	19 (9.6)	17 (13.3)
Health general	13 (8.7)	7 (3.5)	6 (4.7)
Physical health	9 (6.0)	11 (5.6)	8 (6.3)
Treatment	9 (6.0)	4 (2.0)	14 (10.9)
Happiness	8 (5.3)	7 (3.5)	6 (4.7)
Alone	1 (0.7)	3 (1.5)	1 (0.8)

[a] MIF: Melanoma International Forum.
[b] MPIP: Melanoma Patients Information Page.

Each theme was constructed from underlying, more detailed codes. Appendix 1 shows the codes used for each forum and Appendix 2 provides excerpts from posts to provide examples for each code. This provides insight into the construct of each code and displays in more detail which HRQoL aspects the patients spontaneously discussed on the web. Examples of the most-often discussed codes (Table 2) are given below.

Table 2. Total number and percentage of posts mentioning a specific code on each forum (N=476)

Theme and code	Total posts per forum, n (%)		
	MIF[a] (n=150)	MacMillan (n=198)	MPIP[b] (n=128)
Mental health			
Fear, worry, and anxiety[c]	58 (38.8)	78 (39.4)	46 (35.9)
Positive mood	11 (7.3)	17 (8.6)	10 (7.8)
Mental health[d]	3 (2)	16 (8.1)	2 (1.6)
No anxiety or relieve	5 (3.3)	7 (3.5)	4 (3.1)
Stress	6 (4)	4 (2)	4 (3.1)
Not to worry	2 (1.3)	2 (1)	3 (2.3)
Depression	0 (0)	2 (1)	0 (0)
Certainty			
Uncertainty	38 (25.3)	46 (23.2)	20 (15.6)
Hope	13 (8.7)	18 (9.1)	13 (10.2)
Confusion	5 (3.3)	11 (5.6)	4 (3.1)
Guilt[d]	4 (2.7)	5 (2.5)	1 (0.8)
Confident	1 (0.7)	0 (0)	2 (1.6)
Control	2 (1.3)	0 (0)	0 (0)
Healthcare communication			
Lack of information	14 (9.3)	10 (5.1)	4 (3.1)
Informed decision-making	11 (7.3)	5 (2.5)	4 (3.1)
Good information	6 (4)	1 (0.5)	3 (2.3)
Counselling	1 (0.7)	2 (1)	1 (0.8)
Access to information	0 (0)	3 (1.5)	0 (0)
Unfavourable effect			
Unfavourable effects	25 (16.7)	24 (12.1)	19 (14.8)
No unfavourable effects	3 (2)	3 (1.5)	2 (1.6)
Healthcare access			
Waiting time	4 (2.7)	29 (14.6)	10 (7.8)
Finances	6 (4)	7 (3.5)	5 (3.9)
Access medicines	5 (3.3)	4 (2)	1 (0.8)
Access care	1 (0.7)	3 (1.5)	4 (3.1)

Table 2. Continued

Theme and code	Total posts per forum, n (%)		
	MIF[a] (n=150)	MacMillan (n=198)	MPIP[b] (n=128)
Healthcare general			
Good care or good doctors[c]	14 (9.3)	10 (5.1)	14 (10.9)
Bad care or bad doctors	3 (2)	13 (6.6)	4 (3.1)
Disease status			
No spreading	5 (3.3)	4 (2)	1 (0.8)
No evidence of disease	7 (4.7)	0 (0)	5 (3.9)
Progression	2 (1.3)	1 (0.5)	3 (2.3)
Metastasis	2 (1.3)	0 (0)	0 (0)
Support			
Support[d]	14 (9.3)	14 (7.1)	9 (7)
Ignorance	1 (0.7)	6 (3)	1 (0.8)
Lack of support	0 (0)	6 (3)	2 (1.6)
Coping[d]			
Coping[d]	14 (9.3)	22 (11.1)	4 (3.1)
Social life			
Patient network	12 (8)	11 (5.6)	15 (11.7)
Work	2 (1.3)	3 (1.5)	1 (0.8)
Friends	0 (0)	2 (1)	1 (0.8)
Family	0 (0)	3 (1.5)	0 (0)
General health			
Pain	9 (6)	3 (1.5)	3 (2.3)
Diet and appetite	3 (2)	1 (0.5)	3 (2.3)
Good health	1 (0.7)	1 (0.5)	0 (0)
Pain free	0 (0)	2 (1)	0 (0)
Physical health			
Fatigue	5 (3.3)	7 (3.5)	5 (3.9)
Good physically	1 (0.7)	2 (1)	1 (0.8)
Pregnancy[d]	1 (0.7)	1 (0.5)	2 (1.6)
Exercise	2 (1.3)	1 (0.5)	0 (0)
Treatment			
Randomized controlled trials	5 (3.3)	1 (0.5)	6 (4.7)
Good medicines	1 (0.7)	3 (1.5)	7 (5.5)
Drug effectiveness	3 (2)	0 (0)	1 (0.8)

Table 2. Continued

Theme and code	Total posts per forum, n (%)		
	MIF[a] (n=150)	MacMillan (n=198)	MPIP[b] (n=128)
Happiness			
Enjoy life	4 (2.7)	5 (2.5)	1 (0.8)
Normal life	3 (2)	2 (1)	5 (3.9)
Capability	1 (0.7)	0 (0)	0 (0)
Alone[d]			
Alone[d]	1 (0.7)	3 (1.5)	1 (0.8)

[a] MIF: Melanoma International Forum.
[b] MPIP: Melanoma Patients Information Page.
[c] Codes combined as compared with coding scheme used in previous study.
[d] New codes added to the original coding scheme used in previous study.[9]

Fear, Worry, and Anxiety

On all 3 forums, the code relating to *fear, worry, anxiety* was most often discussed (Table 2; Appendix 2). More specifically, on all forums, users talked about being obsessed over moles and being scared about their diagnosis. Other aspects mentioned included, but were not limited to, being anxious about the results (MIF and MPIP), worrying about recurrences (MIF), and the consequences of stopping treatment (MIF and MPIP).

Uncertainty

The second most frequently discussed topic on MIF, MacMillan, and MPIP was *uncertainty* (Table 2). Users were uncertain about many different aspects, such as whether they had made the right decision, whether the medicines would work, if the diagnosis was correct, and how bad the AEs would be (Appendix 2). For example, one user said "[…] any suggestions on […] how not to worry endlessly about the 'what ifs'."

Unfavourable Effects

On MPIP, MacMillan, and MIF the topic *unfavourable effects* was also discussed commonly (Table 2). This focused on the AEs, the complications and the symptoms that the patients experienced. One specific AE that was most frequently mentioned on MIF and MacMillan was lymphedema (Appendix 2). Users also discussed solutions to the AEs and the complications they were experiencing, such as those from the medicines they were prescribed (MIF, MacMillan, MPIP). Not only were the intolerable AEs, complications, and symptoms discussed, but also those that were manageable. Discussions reflected the different degrees of AE presentation

experienced by patients, from manageable to intolerable. For example, 1 user mentioned the following “not the end of the world itching and rash, but it is very maddening and crazy making.”, while another indicated “[...] has a terrible rash on his face head and back. We can LIVE with the rash.”

Waiting Time and Coping

On MacMillan, next to *unfavourable effects*, both *waiting time* and *coping* were often mentioned (Table 2). Coping was also a topic discussed on the other 2 forums (Appendix 2), although it seemed to be discussed to a lesser extent. Users discussed how they coped, for example, with their diagnoses (MIF and MacMillan), with the AEs (MIF and MacMillan), and with their lives in the new normal (MIF and MPIP). Some users indicated how difficult it was to cope with their diagnosis and how they went through denial before being able to accept the seriousness of it all (MacMillan). The long waiting time for appointments and results were also mentioned on all forums (Appendix 2). Users expressed this as: "feels like waiting for eternity", and "the waiting game being the worst". However, some users on MacMillan also indicated that the waiting time was not as long as anticipated.

Hope

Hope was also a code mentioned in all forums. On MIF, a user expressed the following: “I’m getting to the point where I’m believing I could be ok again!” Users also expressed their hope of having scans that showed tumour shrinkage (MacMillan and MPIP) and their hope for medicines that would work (MacMillan and MPIP).

Healthcare

Members shared experiences related not only to their health, but also to their experiences with healthcare, including access to healthcare, lack of information, and making informed decisions (Appendix 2). On all forums, users talked about good and bad experiences with their healthcare. For example, one user posted:

> *I was seen by a new (?), certainly very young doctor who had obviously not read my notes as he had no idea that I was on the Avastin trial. In fact he didn't even know what the trial was and even asked me to spell the drug's name for him!!!! Obviously a very well read young man in his specialist field, not!*

However, good experiences with healthcare were also shared, such as by this user:

> *Had my first PET this week since stage 4 dx, and met with Onc the same day to go over results. She hadn't looked at them yet when we met, so I was pretty nervous. She could tell and just told me these are the first scans and the only bad results would be if there are any new mets that had popped up in kidney, lungs, or any other organs. She said she would be happy with no change, or even if things only grew by a little.*

The subanalysis of MIF subforums (data not shown) showed that *fear, worry and anxiety* was discussed on all subforums, but most often by patients with stage I or II, with 55.0% (33/60; including ND) of the posts mentioning this topic. *Uncertainty* was discussed on all subforums to approximately the same extent (17.6% (6/34) - 32.3% (10/31) of the posts discussed this topic). The topic *unfavourable effects* was more often discussed by stage III and IV patients (25.6% (22/86) including ND) than by stage I and II patients (5.0% (3/60) including ND). ND patients discussed *coping* more often than patients who were not posting on the ND subforums (17.2% (11/64) vs 3.7% (3/82), respectively).

Discussion

Principal Findings

In this study, we showed that melanoma patients and their caregivers discussed many different topics related to HRQoL on public web-based forums. Topics related to *fear*, *worry and anxiety*, *uncertainty*, and *unfavourable effects* were most often discussed. With respect to *fear, worry and anxiety*, some users discussed their worries regarding their moles and diagnosis, which may be most important to patients in the earlier stages of melanoma. Other users discussed aspects related to their fear of recurrence or the consequences of stopping treatment, which may be more relevant to patients in the later stages of the disease. Of note, a caveat of social media is the incomplete information on user characteristics, making it infeasible to determine the disease stage for each user. Many users also discussed aspects related to *uncertainty*. However, this covered different aspects ranging from uncertainty regarding AEs and the effectiveness of the medicines to uncertainty about their diagnosis. Finally, with respect to

discussions on *unfavourable effects*, users shared their experiences with AEs and complications, as well as their solutions.

It is important to realize that the type of social media used may affect the results of a study like ours because social media may be public (anyone may gain access to posts without signing in) or private (where an account is needed before users may gain access to posts). In public sources, users may be less inclined to share personal experiences as compared with private social media sources.[31,32] Previously, we had assessed which HRQoL topics were most important to melanoma patients and their caregivers on private social media by posting a survey on the private social media channels of Melanoma Patient Network Europe.[9] It was shown that *family* and having a *normal life* were the 2 most important HRQoL topics for melanoma patients. In this study, melanoma patients most often discussed topics related to *fear, worry, anxiety, uncertainty*, and *unfavourable effects*. This difference may be because in the previous paper, we actively inquired about the HRQoL aspects most important to melanoma patients, guiding them through a survey, whereas in the current paper, we merely listened to the topics that melanoma patients discussed with each other,[33,34] the latter being a much more inductive approach.

Another aspect that may influence our study results is the overrepresentation of a specific group of users, such as patients with a specific stage of disease or their caregivers discussing the topics most important to them and subsequently driving our results. We previously showed using private social media that melanoma patients with a different stage of the disease find other HRQoL aspects important, as do caregivers.[9] In this study, we confirmed this as our subanalysis of the MIF subforums suggested that different HRQoL topics seemed important to melanoma patients in different disease stages. Subsequently, melanoma-specific HRQoL questionnaires may benefit from taking these differences into account.

Previous research has shown that disease-specific HRQoL questionnaires do not fully represent what patients find important in HRQoL.[9,12,35] For example, the wording in the questionnaires may be different from how patients describe HRQoL aspects; some topics may seem less relevant to patients and some topics may not be included in the HRQoL questionnaires.[9,12,35] Therefore, we evaluated whether melanoma-specific HRQoL questionnaires represented topics discussed by melanoma patients on web-based forums. In both the Functional Assessment of Cancer Therapy-Melanoma (FACT-M) and European

Organization for Research and Treatment of Cancer (EORTC) QLQ-MEL38, some questions related to the theme *mental health* are present.[36,37] In FACT-M, these questions seem to focus on worrying, losing hope, being sad, and feeling nervous. Although in EORTC QLQ-MEL38, they seem to focus mainly on worrying, including worrying about unfavourable effects. In contrast, web-based discussions seem to focus more on the (overwhelming) fear and anxiety of melanoma patients. Regarding *uncertainty*, only EORTC QLQ-MEL38 poses one question *Have you felt able to plan for the future?* However, in web-based discussions, other aspects of uncertainty seem to be more important to patients. Several questions related to *unfavorable effects* are posed in both FACT-M and EORTC QLQ-MEL38, including some questions related to lymphedema. This seems to correspond to the web-based discussions among melanoma patients. Other themes that were often discussed on the web included *healthcare communication* and *healthcare access*. It seems that only EORTC QLQ-MEL38 has questions focusing on these themes. Although these melanoma-specific HRQoL questionnaires have been developed with great care, these findings raise questions about the extent to which these questionnaires cover aspects most pertinent to patients. Therefore, HRQoL questionnaires may benefit from ensuring that topics correspond more to patient experiences, such as including more questions on uncertainty.

It is important to note that although aspects related to AEs may be important for reimbursement decision-making, aspects related to uncertainty and coping are less relevant. However, considering the high psychological burden in the early stages of melanoma, which contrasts with the seemingly benign overall survival outcomes, some topics may become increasingly relevant for HTA as melanoma therapies move from the advanced setting into earlier stages of the disease. These insights highlight the importance as well as the burden that these topics present for melanoma patients across all disease stages, in addition to disease-specific concerns. Healthcare systems, therefore, should be aware that topics such as healthcare communication and access to services can critically impact the HRQoL of patients, irrespective of the given treatment.

Limitations

This study has several limitations. First, we focused on web-based forums, whereas other public, social media channels might provide a different type of insight (e.g. Twitter, public Facebook groups, or blogs). However, not every social media channel is appropriate for gathering insights on a specific topic. For example, information on AEs is not readily available on Facebook or

Twitter.[38] Second, identifying the disease stage for each patient was difficult but has been proven to be relevant as our earlier analysis of stage-specific forums has shown. This could possibly be overcome to a certain degree by using more automated methods of data analysis. In addition, validating authenticity (e.g. verifying whether users actually have the disease they discuss) on the web is difficult.[11,39,40] Third, selection bias may be an issue because the patient population present on web-based forums may be different from the patient population that is not using web-based forums. For example, patients using social media are conventionally better educated,[40,41] more likely to be female,[39,42] and may have a different symptom experience.[43] Finally, web-based forums may update their terms of use at any given time. At the time of collecting the posts, all 3 forums were of public nature and logging in to gain access to the posts was not necessary. However, MIF has changed this and now requires a login to gain access to posts.

Strengths

One of the strengths of this study was the coding of 100 posts from each forum by 2 authors to ensure validity. Analysing qualitative data can be subjective; therefore, agreement between multiple authors when assigning codes is important. In addition, any uncertainties in the posts that were coded until saturation was reached were discussed and resolved by consensus among the 4 authors to further ensure validity. Another strength was determining how often users posted an initial post and a reply post to assess whether one or more users could possibly drive our results. A total of 94.4% (747/791)of users posted only a few posts (≤5 posts) on the forums, suggesting that our results were not driven by one or more users. It seems highly unlikely that the 2 outliers in MIF and MPIP would drive the results, considering the number of posts assessed.

Implications and Conclusions

Patient involvement is becoming increasingly important in HTA, which is especially appreciated during the scoping phase of HTA and for HTA topic prioritization.[44,45] The scoping phase is conducted at the beginning of an HTA assessment, where the technology under assessment, the reference or comparator technology, the relevant study population, and the relevant outcome measures regarding the effectiveness and safety of the technology under assessment are identified.[46,47] In an ideal situation, several stakeholders, including clinicians and patients, should be involved during this scoping phase. The input from patients or their representatives is, for example, important to choose outcome measures that matter to patients. However, the involvement

of patients or representatives may be limited.[48-51] Social media may allow input from a wide group of patients, and may thus provide robust insight into patient experiences. For example, in the scoping phase, social media may be informative in determining which outcome measures would be most important to measure. Social media may not only prove useful in HTA but may also inform healthcare professionals in their understanding of patient experiences and what is important to patients regarding their treatment and healthcare.[52] In addition, issues relevant to patients and which they deal with on a regular basis may be uncovered and could lead to identifying issues that might have otherwise gone unrecognized.[53] In addition, in regulatory decision-making, information from social media may help determine which AEs greatly affect HRQoL, are most debilitating to patients, and which AEs are acceptable to patients.[39,54,55] Therefore, social media may be informative for several stakeholders with varying goals. However, this source of information still needs to become part of the regular data extraction practices of stakeholders. Therefore, clear guidelines are needed for the ethical use of social media data, the limitations that are involved, and the purposes for which this information could be used.

To conclude, it is important to realize that web-based forums are a valuable source to cross-reference the relevance of existing tools and help identify gaps in existing procedures. Social media may contribute to improving the content validity of patient-reported outcome measures, including HRQoL measures. More specifically, current melanoma HRQoL questionnaires may potentially improve patient relevance by adding more items related to fear, worry, anxiety and uncertainty. Social media is a readily available source that can provide fast input from patients with both rare and common diseases. It can be used passively to listen to what patients discuss on the web and to actively distribute questionnaires. In addition, information extracted from social media may support an evidence ecosystem, where existing evidence is used by several stakeholders for different goals. This information source may contribute to a more holistic understanding of the patient's perspective and highlight external factors affecting patient HRQoL. Social media may specifically provide insights for HTA decision-making during the prioritization of topics as well as during the scoping phase conducted before the value assessment of a new health technology.

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Conflicts of Interest
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Authorship Statement
RK designed the study in collaboration with the co-authors. RK collected the data together with authors DD, WG and MB. RK subsequently analysed the data, and wrote the draft manuscript. All co-authors actively contributed throughout the conduct of the study and critically reviewed and approved the manuscript.

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Appendices

Appendix 1. Coding scheme used to code forum posts

Theme	Code
Unfavourable effect	Unfavourable effects
	No unfavourable effects
Alone[a]	
Certainty	Confident
	Confusion
	Control
	Guilt[a]
	Hope
	Uncertainty
Coping[a]	
Disease Status	Metastasis
	No evidence of disease
	No spreading
	Progression
Happiness	Capability
	Enjoy Life
	Normal Life
Healthcare Access	Access Care
	Access Medicines
	Finances
	Waiting Time
Healthcare Communication	Access to information
	Counselling
	Good information
	Informed decision making
	Lack of information
Healthcare General	Bad care/ bad doctors
	Good care/ good doctors[b]
Health General	Diet and appetite
	Good health
	Pain
	Pain free

Appendix 1. Continued

Theme	Code
Mental Health	Depression
	Fear/ worry/ anxiety[b]
	Mental Health[a]
	No anxiety/ relieve
	Not to worry
	Positive mood
	Stress
Physical Health	Exercise
	Fatigue
	Good physically
	Pregnancy[a]
Social Life	Family
	Friends
	Patient network
	Work
Support	Ignorance
	Lack of support
	Support[a]
Treatment	Drug effectiveness
	Good medicines
	Randomized Controlled Trials

[a] New code added to the original coding scheme used in previous study [Makady et al. Social media as a tool for assessing patient perspectives on quality of life in metastatic melanoma: a feasibility study. Health and Quality of Life Outcomes]

[b] Codes combined as compared to coding scheme used in previous study

Appendix 2. Overview of codes per forum and examples to illustrate each code

Code	Forum		
	MIF	**MacMillan**	**MPIP**
Unfavourable effects			
Unfavourable effects	'Sorry your lymphedema is still so bad. I'm still struggling with it, but have gotten to a manageable place with it.'	'I found that lymphedema was way down the consultants' list of concerns… although it was a really big deal for me.'	'But I hit a wall after my 4th infusion. It has kicked my tail with nausea, fatigue, some diahrea, just a bad general overall feeling. So a month after my last infusion, I am still battling side effects. At least I was able to finish my 4 treatments, but feeling pretty rough the last month.'
No unfavourable effects	'She did the same treatment route that you have and like yourself she has not really had too hard of a time with the interferon. Other than being tired, she is pretty good most of the time.'	'So far I haven't had any side effects but monitor myself very carefully, and of course my wife watches me like hawk looking for any changes that I might realise are happening.'	'I didn't have much in the way of side effects through 3 treatments. Fatigue, nausea, stomach cramps and some in transit cancer popping out. For the most part, things went smooth.'
Alone			
Alone	'unfortunate, but still nice to know I'm not alone.'	'I thought this was the best place to look… everyone who comes here is REAL!!!! No medical journals/ papers just real people, which often helps me to feel not as alone!!'	'reminding me so quickly why we do this and we are not alone and we are all fighting together and this thing can be beaten.'
Certainty			
Confident	'[…] so hopefully everything is still clear and good.'	NA	'I'm 32 with a 2 month old baby who was born two weeks before I found the mass in my brain and two smaller spots in my lungs… so, I am not going down without the fight of a lifetime.'

Appendix 2. Continued

Code	Forum		
	MIF	**MacMillan**	**MPIP**
Confusion	'This who thing [has] been a confusing, scary time not only for me but my wife and 2 young daughters.'	'I'm so confused and feel like I've been left in limbo'	'We haven't gotten a second opinion - should we? and if so where? Who?What questions should we be asking right now?We are trying to move past shocked and denial stages to take action.'
Control	'It is so hard to keep emotions under control.'	NA	NA
Guilt[1]	'As for tanning beds, yes, I started going at age 15, stupid! I went every winter 1-2 x a week for years.'	'I feel guilty complaining as I know there are others suffering more than me...'	'And then there will be the lingering fear of the unknown and the guilt that so many special people have died of this disease including [...] and [...] and so many others. I volunteer at a nonprofit that offers free support for cancer patients and their families. It helps.'
Hope	'My derm said that we wouldn't go back in and cut deeper unless we find something moderately dysplastic or worde. Yay!!! I'll be seeing my oncologist on the 15th of Jan for a standard follow-up, and feel certain that EVERY LIL THING, GOIN' BE ALRIGHT.'	'Fingers crossed tomorrow's scans are clear.'	'but, like i just said IM STILL HERE! that alone i keep telling myself haha... Its all good, im in the fight & hopefull...'
Uncertainty	'So I am going through anxiety again... the waves of fear, and what ifs, and when and how...'	'I have been told that I have a 50:50 chance of recurrence. I feel as though I spend my whole time pre-occupied watching and waiting for 'it' to happen.'	'I'd say the big thing with nivo is uncertainty. Is my knee pain because I'm getting older and did too much or a side effect? Is my stomach upset due to stress or a side effect? The joint pain is probably cause I overdid it.'

Appendix 2. Continued

Code	Forum		
	MIF	**MacMillan**	**MPIP**
Coping			
Coping	'I think that I am still in the process of accepting the diagnosis and trying to make adjustments (like sun avoidance btw. 10-4pam) and take them in stride.'	'I apologise if this is selfish but for the last 10 months I have been finding it difficult to cope. I put on a smiley brave face with my husband and children, am back at work but just cannot face discussing my concerns directly with anyone.'	'We are trying to move past shocked and denial stages to take action.'
Disease Status			
Metastasis	'[…] Frozen all came back good, until 2 days later they called me in and said I had micro mets to the left one and so I had surgery again that week, with removal of 10 nodes…all negative.'	NA	NA
No evidence of disease	'But I am alive and I am NED for now.'	NA	'The oncologist was happy to announce she considers me NED!'
No spreading	'As usual the moles I was nervous about were normal. I have to remember that change isn't necessarily cancerous. For me it's normal to have the pigmentation on my moles change a bit.'	'I got my results on Thursday and everything has stayed the same as the last scans 8 weeks ago, although there has been no shrinkage, there has been no growth either, so great news!'	'I just got results from my most recent scan, and I am celebrating a full year since my last surgery which cleaned house of my major tumors. All clear, with no new progression.'

Appendix 2. Continued

Code	Forum		
	MIF	**MacMillan**	**MPIP**
Progression	'Well just back from Don's colonoscopy & even though oncologist after reviewing PET was pretty hopeful would not be melanoma .... It is back. He had 14 montsh NED after IPI.'	'I have a stage 4 melenoma, about 3 weeks ago mine was found to have spread into one of my lungs!	'I had been on Keytruda for 3 months then liver progression, then TAF/ MEK (short stay due to side effects), now I feel another in transit in my scar. These in transits seem to keep popping up in my same scar area even though I have had 2 WLE and CLND. Immunotherapy and Targeted Therapy don't seem to be working either. I am getting discouraged trying treatments only to see more mets and progression. I have a CT Scan and appt next week, need some positivity from long term Stage 4 warriors on this site as I am becoming discouraged with what seems like a downhill battle for me.'
Happiness			
Capability	'The idea of not being able to go running again ever in my life if painful.'	NA	NA
Enjoy Life	'For most of us it's a huge wake up call to what is really important in life and you learn not to take anything for granted.'	'I can live with the groovy compression sleeve but don't want to have to give up all the things that make me happy.'	'I felt so incredibly lucky today. I was able to piddle about in my yard with the love of my life, feel the warming breeze on my face and see one more spring. Melanoma is more than able to take that moment, this day, from any of us. So as I tried to soak in the spring beauty that life afforded me once again, I thought about things.'

Appendix 2. Continued

Code	Forum		
	MIF	**MacMillan**	**MPIP**
Normal Life	'Just on the downside now and I can't wait to feel normal.'	'I still have my moments when I worry about the future and the usual paranoia over swollen glands etc, but generally I am back to normal.'	'He is currently NED, we hope he stays that way forever! He works, goes hiking, does everything without any problems, just like before'
Access Care	'Also, before we started the trial we contacted MD Anderson, sent them all the scan results, blood work, etc. for second opinion and they said they can treat Dave there but we have to relocate to Huston and pay for everything.'	'It seems in my area anyway that there are a lack of services / resources for this condition.'	'In all my research, it seems that the nursing facilities in commuting distance for my mom don't have much information on how they help cancer patients. It has also been extremely challenging to find a nursing home willing to administer the targeted therapy medication my dad needs (they are taken orally, but due to his difficulty swallowing, they have been putting them through a feeding tube).'
Access Medicines	'In the meantime I tried to join ONCOVex but it was a no go because I was not an UK citizen!'	'I really hope that we can get this decision reviewed & Yervoy accepted - it's the only hope we have & it's cruel to deny us our lives - particularly younger sufferers & their dependant families. The cost of the drug must surely be outweighed by the cost to the system - when a young parent loses their life to the disease & the family can't afford to live without support from the state.'	'At the time my only option was interferon or watch and wait. '

Appendix 2. Continued

Code	Forum		
	MIF	**MacMillan**	**MPIP**
Finances	'Though I am B-RAF positive and accepted from the phase 3 trial my insurance is causing trouble because it is just a trial ... So I am fighting but preparing a plan B, C and D!'	'it is awful worrying im considering trying to go private if i can afford it to be seen quicker and get a diagnosis back as me and my family are numb.'	'No, my insurance denied the $8,500 bill. I don't know if I'll get billed by [hospital]. I was not made aware of the cost prior to the test being done.'
Waiting Time	'I am going to [hospital] for this. The wait to get into [hospital] has been about a month, which has me very anxious.'	'Think my anxiety is through the roof having waited 7 weeks to get the result.'	'Oh gosh-isn't waiting the worst! I'm playing that waiting game right now and every time the phone rings I take a deep breath...you know what I mean!'
Healthcare Communication			
Access to information	NA	'They sent out a letter for a follow up appointment on 09/11/2017.Yesterday I received a letter bringing forward my appointment to 03/11/2017. This immediately sent my mind in to overdrive so I called the Dermatologist clinic who told me they had results but couldn't tell me over the phone. Given that I live 100 miles away from the hospital I contacted my GP and explained.I received a call back from my GP an hour later, telling me I've got Melanoma. He was unable to tell me any more than that.I'm now worried sick, my whole world feels like it's being turned upside down.'	NA

Appendix 2. Continued

Code	Forum		
	MIF	**MacMillan**	**MPIP**
Counselling	'I'm not a particularly modes person (being a former actor will do that), but I'm 53, male, and a tad (hee) overweight, so standing there naked for my early -30s very attractive female derm is a tad offputting, BUT, it beats dying of cancer!'	'I had severe depression a few months after my diagnosis last year. My GP referred me to a counsellor, I was sceptical at first but I went as I decided that it was worth a try. I can honestly say, it helped a great deal. My counselling finished around Christmas time and I am now feeling 100% better.'	'I think I will discuss with her my thoughts/ worries. Hoping she can take her 'dr' hat off long enough to put herself in my shoes and think about what she would want done.'
Good information	'Doctors do not talk about the little things that can make a hospital stay so miserable, like your stool. I now feel much better prepared for my dissection.'	'Thanks for the checkup and excision info - I got told a bit about what would happen at an excision when I had the biopsy, but also got told "but that won't happen" so didn't pay as much attention as I should have, in hindsight.'	'Given my diagnosis I very much look to be informed so as to effectively manage my care '
Informed decision making	'He is an amazing man. He was very positive and encouraging. He was actually encouraging no surgery – but my husband and I still felts that is was the best coarse for use – and [Doctor] was ok with that too.'	'They reiterated that the SLNB was completely optional and up to me - I very nearly changed my mind but decided to go ahead in the end.'	'At the time, I think it was standard of care to recommend a SLNB for any lesion greater than 1mm. I was staged at that point, 3A, due to the two positive lymph nodes. After the SLNB, I transferred to [hospital] for my care. I discussed the CLND with my surgeon, [doctor] who reviewed the procedure versus watch and wait, I opted for the,procedure with no additional positive nodes. The only other testing was for BRAF as I recall.'

Appendix 2. Continued

Code	Forum		
	MIF	**MacMillan**	**MPIP**
Lack of information	'[...] Did anyone met doctors like mine? I feel they are ignorant and not serious. They don't seem to put any effort in communicating with me and even when I ask educated questions, they brush me off like it's nothing. Oh, and about the mole on my earlobe. I asked the surgeon about it and he said Oh, of course it's melanoma. It's just that we are not doing anything about it right now. We should wait and see of it comes back. [...]'	'Yes, it has been quite an ordeal and frustrating not to have had the information about the blood clots. I've saved every document I have been given, but no text on blood clot risks and no in-person warning from anyone.'	'Now that I know better, there won't be any additional shave biopsies in my future! I had no idea going in or I would have requested something different.'
Healthcare General			
Bad care/ bad doctors	'Honestly, I feel like my doctor blows me off a lot too, and after reading this thread I am once again realizing I am my own best advocate.'	'I had a delay in my diagnosis as my Gp dismissed mine the first time 8 went. .it took 10 months before I got mine removed. I can't help but wish I had insisted much sooner.'	' I had to push very hard tor a biopsy and it ended up saving my life. Push for the procedure and find out for certain it's nothing.'
Good care/ good doctors	'My oncologist thinks that a month of interferon is good enough. He's been careful in counselling me and watching for depression, which has been only for a few days. His staff is also watchful, too.'	'My specialist nurse is great I call her with everything! And she really makes me feel at ease and explained everything so well to me she also speeds things up as much as she can, I have two children, mine are 2 & 4, so really I wanted everything over with as quick as possible to get my recovery started!'	'At the beginning we were sure we'd get a second opinion, but after inhaling as much info as possible, it was clear that treatment would be basically the same anywhere, and our experiences at the center were extremely positive, so there was no need.'

Appendix 2. Continued

Code	Forum		
	MIF	**MacMillan**	**MPIP**
Health General			
Diet and appetite	'He's also changed his diet (I listened to the audio book Anti-Cancer on my drive to visit, and it had some great suggestions in this regards), and is taking some supplements like modified citrus pectin.'	'Have you considered the Vit B17 route? I have seen a lot of blogs totally dismissing the idea and yet I have looked into it extensively I believe there could be huge benefits! I guess I also feel anything is worth a shot and some of the testimonies are incredible!'	'So far I'm doing ok, just not a lot of appetite yet and very tired.'
Good health	'pretty good most of the time'	'I'm very happy to say that I am still feeling fit & healthy & my consultant is very happy with my rude health!'	NA
Pain	'It took a long time to recover from these surgeries with a lot of nerve pain but after 1 yr I was doing better. For the past 6 wks or so I have had almost non stop pain in my Lt thigh. Feels like nerve pain and is really painful in my 3 and 4 yr old incisions. If I ignore it it become sunbearable and I get a lot of knee pain but usually doesn't affect my lower leg.'	'Feeling better in myself, although still rather sore, and now just have to wait. '	'Hurting bone, joints and muscles…. Help HELP: I have been on OPDIVO for 10 treatments so far and 16 more to go, the past two weeks, I have had muscle/bone pain all over, My neck, arms, hands, fingers, hips and legs. Just sitting, I feel so tight but when I move, I just cringe with the aching pain. Anyone else have this issue and what things have helped. I have tired 1000 mg Bayer back and body, little relief. I have also taken 800mg Motrin, again little relief. So, will this go away or is it now with me for the long hall.'
Pain free	NA	'My arm isn't tight though and it feels very comfortable, with no after pain.'	NA

Appendix 2. Continued

Code	Forum		
	MIF	**MacMillan**	**MPIP**
Mental Health			
Depression	NA	'Hi [user] just to say the blue will fade in time, well mine did!'	NA
Fear/ worry/ anxiety[2]	'The fear is the worst and we all live with it every day.'	'I am totally paranoid about being outside uncovered despite having factor 50 on.'	'This is a roller coaster ride and not the good kind. I remember feeling like I had gotten on an express train and couldn't get off. Once my diagnosis came down I was constantly reeling.[…]'
Mental Health[1]	'[…] yes I am appalled that on some issues I can't seem to get a straight answer. Maybe I ask too many questions??? But that helps me keep sane with this diagnosis!!!'	'I am not sleeping at all well now days, Its not the hot weather and don't think its anything to do with the treatment, it might just be that my head is messed up with everything that all of us on here are going through.'	'The oncologist was happy to announce she considers me NED! She then told me that since I had the brain tumor the last time I was off treatment that we needed to continue with the Opdivo at least another year. Despite the great news I'm hesitant to be too happy and reluctant to consider myself in the clear. I worry that this will not be my last dance with this devil. I'm still bearing the scars from the brain surgery and radiation. My right foot is still numb from the crainiotomy. I'm still not mentally whole.'
No anxiety/ relieve	'I received the biopsy report on the toe mole this past Thursday and it came back benign. I was so relieved (and happy) I wanted to break out in an Irish Jig…despite the painful toe.'	'I have fortunately just had my results this week from my SLNB and WLE which were both clear (hooray)'	'I was extremely relieved at the time because I knew the biopsy report was about as good I could have hoped for, short of it being melanoma in situ.'

Appendix 2. Continued

Code	Forum		
	MIF	**MacMillan**	**MPIP**
Not to worry	'[...] This helped put my mind at ease, as I was really scared.'	'You wonâ€™t believe it but nine months on and I am NOT spending all my waking hours worrying. In fact only when I get my 3 month check does it come to mind. Or occasionally when log onto the forum'	'(One question I always ask myself - if I hadn't had a melanoma diagnosis, would this lump/bump/lesion bother me??? Because if the answer is no, then it's probably still the right answer even after your diagnosis).'
Positive mood	'I had my side ecission in November 2009 and in general things have been healing nicely and I feel wonderful.'	'There is nothing I like more than beating statistics'	'I've been lucky, and have been my own advocate for my care.'
Stress	'I can't sleep or eat. I'm frozen.'	'I too thought dreadful things and physically made myself unwell with the stress and panic.'	'I have struggled to get the replacement doses for my missing hormones correct. I have limited energy and my tolerance for stress had dropped to close to nothing.'
Physical Health			
Exercise	'I have found running to be one of the most helpful things for my lymphedema. Granted, I won't be running any marathons, but 10k's are doable and I might even try to work up to a ½ marathon but we'll see. The key for me is to not overdo it too quickly. It took me a long time to VERY slowly build up to running 5 miles without pusihing too hard.'	'My son, whom just entering teens, so not very sympathetic said' mum you're walking like an old lady' I'm determined to improve physical health asap especially as spring summer approaches.'	NA

Appendix 2. Continued

Code	Forum		
	MIF	**MacMillan**	**MPIP**
Fatigue	'Some of the side effects have been a little difficult. Mostly the fatigue. I used to work 10 hour days 5 days per week. That has not been possible, but I'm blessed to work for a supportive company.'	'Treatment made me tired and it's a bit of a vicious circle, tiredness makes you more inactive and increases tiredness !!'	'My only complaint has been fatigue. I have tolerated this stuff better than most. I refuse to let the fatigue win.'
Good physically	'I feel physically good [...]'	'Tell [user] that in my case, the only plus about melanoma (if you could call it that) is apart from the normal after op pains I have never actually suffered physically. Perhaps a bit mentally as it can bombard the senses on a bad day.'	'[...]My husband feels great and in fact is playing 18 holes of golf today.'
Pregnancy	'My new worry is, my husband and I would really like to have another baby, we always wanted 3 kids! But the doctors know I got the Melanoma when I was pregnant with my 2nd son and I am concerned that if I get pregnant again the melanoma will come back or I will get a different type of cancer. I would really like to have another baby but it was soo hard dealing with the cancer and surgery while having a newborn. Do I take the chance or not?'	'I was pregnant in that time so I didn't bother much about it (I had no idea it can speed the things up). Two months after my baby was born I went to GP and showed him my mole, however 'nothing to worry about.'	'i have many of the same concerns and am having a tough time wondering if I'll be able to carry another pregnancy. (Daughter is almost 1 yr, she was 7 months when I diagnosed stage 3a).'

Appendix 2. Continued

Code	Forum		
	MIF	**MacMillan**	**MPIP**
Social Life			
Family	NA	'fabulous emotional support from my friends and family. '	NA
Friends	NA	'Thank goodness for my fabulous friends who came round to help me with the babies and to keep me company.'	'I had the fortunate experience to have a very dear friend from England, who immediately came to help and stayed with me for 6 months.'
Patient network	'I cannot emphasize how much I appreciate the support and guidance I have received on this forum. I cannot imagine where I would be right now without it.'	'its good to share views and feelings on here isn't it I don't think anyone who hasn't gone through any of this can properly understand as I know I didn't before.'	'The encouragement and stories really helped! I'm not much of a poster but check out the site every other day or so. My onc is always amazed at the facts and information I come in with at my appts. It's thanks to all of you.'
Work	'[…] I'm blessed to work for a supportive company.'	'I now have secondary adrenal insufficiency and I no longer can cope with the highly stressful parts of my job and the travelling. However, my employers have been great and I am still working three years after a pretty poor prognosis.'	'So give me the good, bad and ugly about Keytruda. I know everyone reacts differently, but I had no idea what to expect last time and I really would love to know more this time. I have a two year old son and husband, which is different from ten years ago and I am hoping I can still function to work and be a mom.'

Appendix 2. Continued

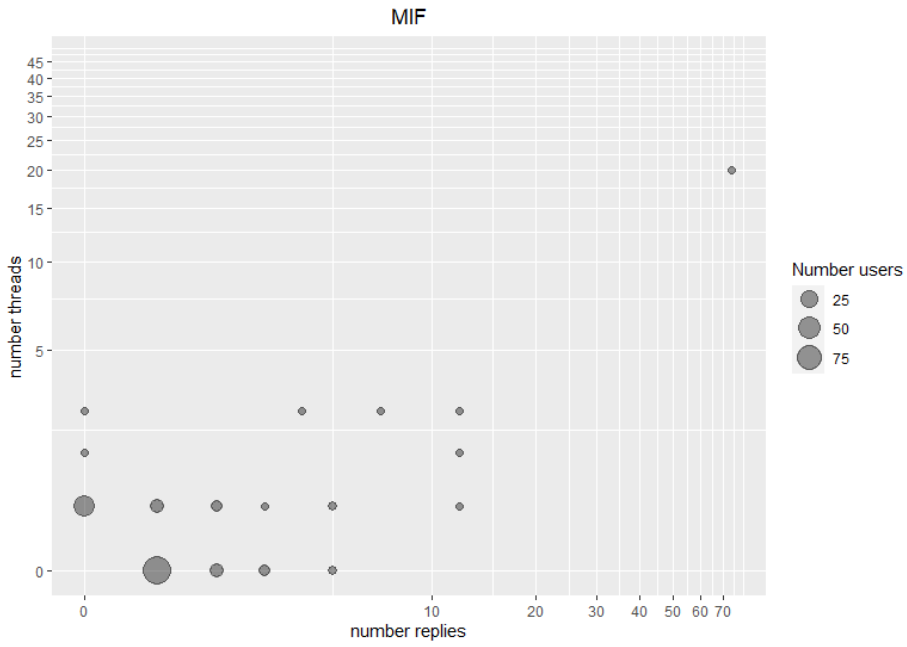
Code	Forum		
	MIF	**MacMillan**	**MPIP**
Support			
Ignorance	'I can't tell you how many people, when I tell them I had the melanoma, say, Oh, I had one of those and I just stare at them. Then I say, Really? Where? Did they get it early? And they shrug their shoulders and say, Oh, I don't really remember. Because, they WOULD remember a melanoma...they HAD some sort of pre-cancer. Argh.'	'I also have to smile through gritted teeth when I'm told that I'll back to my old self soon etc! No one understands how the lymphatic system works (I didn't until this) so I can never be my old self !'	'No one seems to understand how hard it is, especially when im 28!!'
Lack of support	NA	'Not getting much emotional support from my other half who doesn't really talk just says "it will be fine".'	'I don't have a big support group because we moved from Texas to Seattle a few years ago.'
Support	'Thank you all for the feedback and support I have received. I really do appreciate it and don't know how I would have kept my self sane without having this board to bounce things off of.'	'but my point is, i sometimes feel very alone, and you guys, although i've never met u offer such great support and comfort at times wen i feel quite lonely, thank you, and wen u all have so much going on too, i think its safe to say there are some remarkable people on this forum.'	'Rather than get into any more details, I want to just thank those who supported me, and shared their wisdom and experience throughout these years'

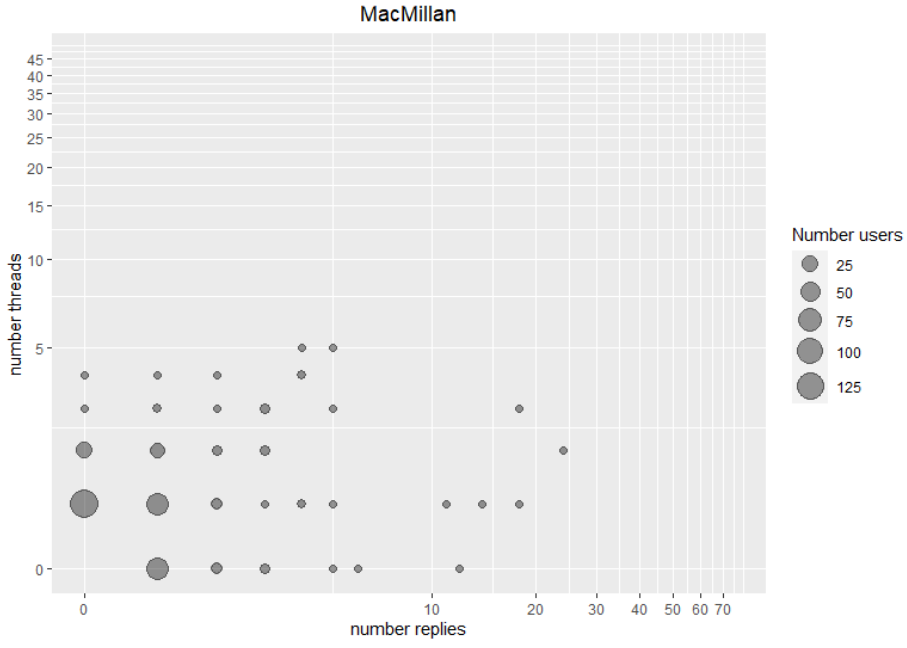
Appendix 2. Continued

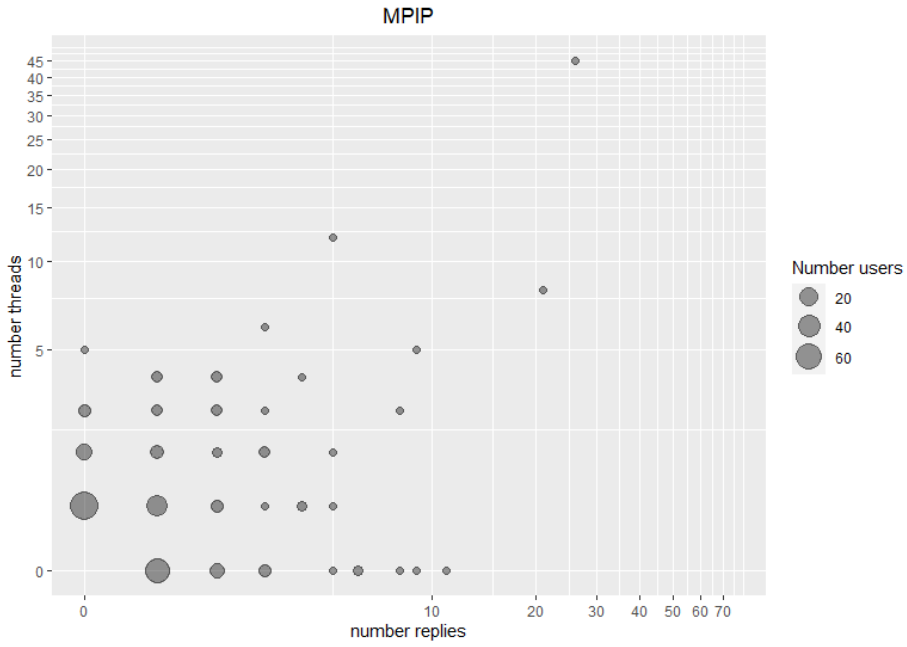
Code	Forum		
	MIF	**MacMillan**	**MPIP**
Treatment			
Drug effectiveness	'I agree that Intron, or interferon, is not the be all, end all of drugs. [...]'	NA	'[...] Went to emergency room and they diagnoised with Pneumonia, spent 3 days in hospital with massive IV antibodies. Turns out it is not that but Pneumonitis caused by treatment. At home on oxygen and have appointment on WED. Doc said that it is a reaction to drug. Up until this point I did not have respect for how powerful the drug was, because side effects were minimal.'
Good medicines	'She did the same treatment route that you have and like yourself she has not really had too hard of a time with the Interferon. Other than being tired, she is pretty good most of the time.'	'I had Ipi.I was incredibly lucky in that Ipi worked for me. It activated my T-cells, which destroyed my tumours. I am in the group called 'complete responders'.'	'I'm stage IV and started with the ipi/nivo combo and it worked very well for me. I can't say it was a walk in the park but much better than the treatments for the other cancer types. I'm currently on nivo only and I tolerate it fairly well.'
Randomized Controlled Trials	'I starting to question whether the medical field really care about the people or just the reserach they can do on us.'	'i'm stage 3b and was only offered the avastin trial which i refused cos of theÂ fear of it stopping me being accepted onto any further trials which are more affective down the line.'	'I am afraid they will knock me out of the study but have adrenal failure and hypopituitarism is not healthy at all.'

MIF: Melanoma International Forum; MPIP: Melanoma Patients Information Page; NA: Not Applicable

Appendix 3. Number of threads and reply posts of each unique user posted on each forum for the posts assessed






MPIP
number threads
45
40
35
30
25
20
15
10
5
0
0
10
20
30
40
50
60
70
number replies
Number users
20
40
60

Part C

Potential of indirect treatment comparisons for health technology recommendations

Chapter 7

Influence of indirect treatment comparisons on reimbursement recommendations

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Manuscript in preparation

Abstract

Objectives: To evaluate the use of indirect treatment comparisons (ITCs) in Health Technology Assessment (HTA) in the Netherlands and England.

Methods: Initially all HTA reports on pharmaceuticals published between 2015 and 2019 by the Dutch National Health Care Institute (ZIN) and English National Institute for Health and Care Excellence (NICE) were included. Subsequently, for in-depth analysis only full reports of ZIN were included while for NICE 100 reports (random sample; 20 per year) were included. Based hereon, comparator pairs were defined for relative effectiveness assessments (REAs), and treatment-indication pairs for cost effectiveness assessments (CEAs) and final recommendations.

Results: Between 2015 and 2019 ZIN assessed 166 reports and NICE 258 reports, of these 35% and 55% included an ITC, respectively. While NICE in 59% of reports evaluated oncology treatments, this percentage was much lower for ZIN (17%). The in-depth analysis (106 reports from ZIN and 100 from NICE) demonstrated that the use of ITCs had a pronounced effect on the outcome of the REA, where more commonly equal benefit was demonstrated (54% and 42% for ZIN and NICE, respectively) while using only direct evidence led more often to added benefit (58% and 66% for ZIN and NICE, respectively). Use of direct or indirect evidence did not show pronounced differences in CEA conclusions or final recommendations for ZIN or NICE. Analysis of the types of ITCs showed that ZIN mostly evaluated unadjusted ITCs while in NICE reports network meta-analyses were most common.

Conclusions: Analysis of ZIN and NICE reports showed that ITCs are very common and may particularly affect the REA outcomes. The ITC methods used differed between the two agencies which may depend on the type of pharmaceuticals assessed but also on their assessment process. Our results support a further alignment of the process and methods of ITCs used especially considering the foreseen EU HTA regulation which ensures consistent comparative evaluation of new pharmaceuticals.

Highlights

HTA agencies in the Netherlands and England regularly evaluate indirect evidence as a basis for reimbursement recommendations. Although direct evidence will remain the gold standard for HTA, especially for REA, the use of indirect evidence will become more important as the HTA regulation (HTAR) created by the European Union (EU) is foreseen to start in 2025.

HTA agencies in the Netherlands and England used different methods to evaluate indirect evidence, where the Netherlands often evaluated naïve ITCs and England often evaluated NMAs. These differences are also expected to exist between HTA agencies within the EU. A greater level of alignment on acceptable ITC methods between national HTA agencies in Europe is necessary before the EU HTAR comes into effect, and to ensure timely and equal access to new pharmaceuticals across Europe.

Introduction

Before new pharmaceuticals can reach patients, the European Medicines Agency (EMA) is responsible for the scientific assessment of the efficacy, safety and pharmaceutical quality of these pharmaceuticals in order to determine whether market authorization should be granted. Subsequently, pricing and reimbursement recommendations are based on an assessment of the relative effectiveness (REA) and cost-effectiveness (CEA) of these pharmaceuticals. This assessment is mostly conducted by national Health Technology Assessment (HTA) agencies. Often similar clinical data is used by regulatory bodies for market authorization and HTA agencies for reimbursement recommendations which preferably originate from randomized clinical trials.

For market authorization a new pharmaceutical is preferably compared to a placebo or to a pharmaceutical already used in clinical practice for the same indication. The comparator for reimbursement recommendations, on the other hand, ideally is the current standard of care. However, standard of care may differ between countries due to differences in national guidelines or availability of a pharmaceutical. Because most pivotal trials for new pharmaceuticals for market authorization and reimbursement recommendations only include a limited number of comparators, indirect treatment comparisons (ITCs) may be necessary to compare to other relevant comparators.[1] ITCs facilitate the indirect comparison between two treatments (e.g. A and B) when head-to-head (direct) comparisons are unavailable. This may imply that for instance a third intervention (e.g. C) is used to which the two treatments (A and B) were directly compared in a trial setting.[2] Although ITCs are not preferred, they are widely accepted when direct comparisons do not exist.[1,3]

National HTA agencies may differ in their willingness to accept indirect evidence as well as in their preferences regarding the specific methodologies used, nevertheless, they may have to rely on ITCs when head-to head trials against relevant comparator(s) are unavailable.[4-6] Detailed guidance on the conduct of ITCs is published by some HTA agencies, but not by others.[5-7]. However, because of the implementation of the European Union (EU) HTA Regulation (HTAR) in which joint clinical assessments (JCAs) are foreseen to start in 2025,[8] there is an urgent need to attain more alignment on how to perform and assess an ITC. Currently, EU guidelines on indirect comparisons are in revision.[9]

The aim of this study was to assess the acceptability of ITCs by two HTA agencies and whether there was a relationship between a reimbursement recommendation and the use and outcome of ITCs. Therefore, we set out to evaluate the influence of ITCs on HTA recommendations in the Netherlands and England by answering the following three research questions: 1) How often are reimbursement recommendations based on ITCs? 2) Which reimbursement recommendations result from the use of ITCs? and 3) Which methods for ITCs are accepted for reimbursement recommendations?

Methods

Selection of assessments

All reimbursement recommendations of pharmaceuticals conducted between 2015 and 2019 by the National Health Care Institute (ZIN) in the Netherlands and the National Institute for Health and Care Excellence (NICE) in England were identified. Each HTA report was examined to determine whether an ITC had been used to inform the REA and/or CEA.

In case of the Dutch recommendations, we included recommendations that were the conclusions from both full and marginal assessments. It is important to note that in the Netherlands the process of reimbursement recommendations for intramural and extramural pharmaceuticals differs. Intramural pharmaceuticals are assessed using a risk based approach based on the estimated budget impact, where some pharmaceuticals become directly available or are assessed by the health insurers[10] while others first need to be assessed by ZIN and are included in the waiting lock.[11,12] Extramural pharmaceuticals all need either a marginal or full assessment. Marginal assessments do not contain a full REA or CEA and are conducted when a new extramural pharmaceutical is assessed on the interchangeability with a pharmaceutical which is already part of the reimbursement system (e.g. a new chemical entity within a class of pharmaceuticals). For these marginal assessments we identified whether an ITC had been part of the evidence used for the recommendation, but no further analysis was done. Full assessments always include a REA, but not always a CEA (e.g. a CEA is only included when the REA indicates a new pharmaceutical is of added value). Full assessments were included for detailed analysis. RK and MdV independently assessed 13 reports published in 2017 and 11 reports published in 2018 for eligibility. No discrepancies between the assessors were evident in the identification of reports including indirect evidence. However, in 25% of

the reports minor differences were apparent regarding the outcome measures identified (e.g. one or two outcome measures were not mentioned by one of the assessors). For those discrepancies author RK rechecked the report and made the final decision, since these minor differences are unlikely to affect the final results of this study no additional authors were involved herein. Data from the remaining reports were extracted by author RK.

In case of the English recommendations, we decided to only include a subset of reports for further data extraction due to the large number of reports published by NICE (258 reports between 2015 and 2019). A random sample of 100 reports (20 per year) was selected of which 50 reports included only direct evidence and 50 included indirect evidence. Each of these reports included a REA and CEA, since NICE requires both for reimbursement recommendations. Data from these NICE reports were extracted by four authors (RK, DDa, CB and EL). For validation purposes, a random sample of 20% of these extractions was independently checked by a second assessor (DDa, CB or EL). In addition, for consistency purposes, author RK was involved in extraction from both ZIN and NICE reports.

Data extraction

Data from each included report published by ZIN and NICE were extracted using a predefined data abstraction form. The information collected included, but was not limited to: general information, such as the PICO (e.g. the patient population, intervention, comparator and outcomes); and information related to the ITC, including the method used. In some reports in which both direct and indirect evidence was included information for both types of evidence was collected. The reimbursement recommendation, as well as the REA and CEA conclusions were also extracted.

Some reports included REAs in which multiple comparators were included, resulting in multiple REA conclusions. Therefore, data regarding the REA were extracted separately for each comparator pair from the included reports. Additionally, some reports issued more than one reimbursement recommendation since multiple treatment-indication combinations were included in one report.[13] Data regarding the reimbursement recommendation and the CEA were extracted separately for each treatment-indication combination.

Outcomes of the assessments

Conclusions from REA were categorized as 'added benefit' (indicating an added therapeutic value/benefit of the new pharmaceutical versus the comparator), 'similar benefit' (indicating a similar therapeutic value/benefit of the new pharmaceutical versus the comparator) or 'lesser benefit' (indicating a lesser therapeutic value/benefit of the new pharmaceutical versus the comparator).[14,15] In reports published by ZIN these categories are mentioned, in those published by NICE this is done slightly different (e.g. a new pharmaceutical is mentioned to work as well as, or is more clinically effective, or is not as effective as the comparator). In a few reports evidence was ambiguous or not enough evidence was available to make a conclusion regarding REA, therefore the category 'other' was used.

Conclusions from CEA were categorized as 'cost effective' and 'not cost effective'. In a few assessments published by ZIN and NICE it was stated that no valid estimate could be calculated or no conclusion was given, therefore the category 'other' was used. It is important to note that ZIN and NICE use a different cut-off value for cost-effectiveness. In addition, in England price negotiations may be conducted before the CEA has been assessed.

Reimbursement recommendations were categorized as 'positive' (recommended without restrictions), 'restricted' (recommended with restrictions) or 'negative' (not recommended).[14,15]

Reports were categorized based on the type of evidence, where 'direct' reflects reports including only direct comparisons and 'indirect' reflects reports including at least one indirect comparisons. Therefore 'indirect' reports may include a combination of 'direct' and 'indirect' evidence.

The methods used for indirect comparisons were categorized into four categories. The first category 'naïve ITCs' are unadjusted ITCs where no corrections or adjustments are made. In other words, the results of two trials are compared to each other as if these were extracted from a single controlled trial.[16] Category two are 'adjusted ITCs' and includes ITCs comparing no more than two trials to which any type of correction or adjustment have been made using statistical methods. This includes, but is not limited to, the adjusted single indirect comparison proposed by Bucher et al[7] and matching adjusted indirect comparisons (MAIC) which is an extension of Bucher's method using individual patient data to adjust for patient differences between studies.[1] The third category are 'NMAs' that

allows to simultaneously compare more than two treatments to each other,[16] in such comparisons some adjustments can be made and both direct and indirect evidence may be incorporated.[2,17]. In some reports it was unclear which specific ITC method had been used and therefore the fourth category 'unclear' was used.

Results

Type of reports

Between 2015 and 2019 a total of 166 and 258 reports were assessed by ZIN and NICE, respectively (Figure 1). Of the 166 reports published by ZIN a total of 60 reports were marginal assessments and 106 reports were full assessments. A total of 51 pharmaceuticals were assessed by both ZIN and NICE for the same indications.

Figure 2 shows for which indications ZIN and NICE had published reports. Pharmaceuticals for oncology were assessed in 59% (152/258) of reports by NICE. ZIN most often assessed pharmaceuticals for oncology (17%; 28/166) and for endocrine, nutritional or metabolic diseases (17%; 28/166). Orphan diseases were the focus of 14% (37/258) and 17% (29/166) of reports from NICE and ZIN, respectively (data not shown). A few reports included Advanced Therapy Medicinal Products (ATMPs), 3% (7/258) of NICE reports and 2% (3/166) of ZIN reports (data not shown).

Indirect treatment comparisons

A total of 35% (58/166) and 55% (142/258) of reports included an ITC, for ZIN and NICE respectively (Figure 1). Of the 106 full assessments published by ZIN a total of 48 (45%) included an ITC (data not shown).

In-depth analysis

This analysis includes the 106 full reports assessed by ZIN, and a random sample of 100 (20 per year) reports published by NICE of which 50 reports include only direct evidence and 50 reports include also indirect evidence. Since multiple comparators were included in some REA reports, comparator pairs were identified. A total of 178 comparator pairs for ZIN were included (61% included indirect evidence), and a total of 231 comparator pairs for NICE (72% included indirect evidence). Additionally, treatment-indication combinations were defined due to some reports issuing more than one reimbursement recommendation. These were also used in the analysis of the CEA conclusions. A total of 111 and 129 treatment-indication

combinations for ZIN and NICE, respectively, were included (see Figure 1 and Table 1). Of the treatment-indication combinations, 46% included indirect evidence for ZIN and 57% for NICE.

Table 1 shows the REA conclusions for each of the comparator pairs from the included reports. Added benefit was demonstrated by ZIN in 58% of comparator pairs when only direct evidence had been used, and in 29% when also indirect evidence was used. In the REA assessed by NICE added benefit was the conclusion in 66% of comparator pairs when only direct evidence had been included, and in 52% when also indirect evidence was included. Similar benefit was concluded in 13% and 25% of comparator pairs including only direct evidence, and in 54% and 42% including indirect evidence by ZIN and NICE, respectively.

The detailed analysis of CEA conclusions is presented in Appendix 1. The use of direct or indirect evidence did not lead to any pronounced differences in CEA conclusions for either ZIN or NICE.

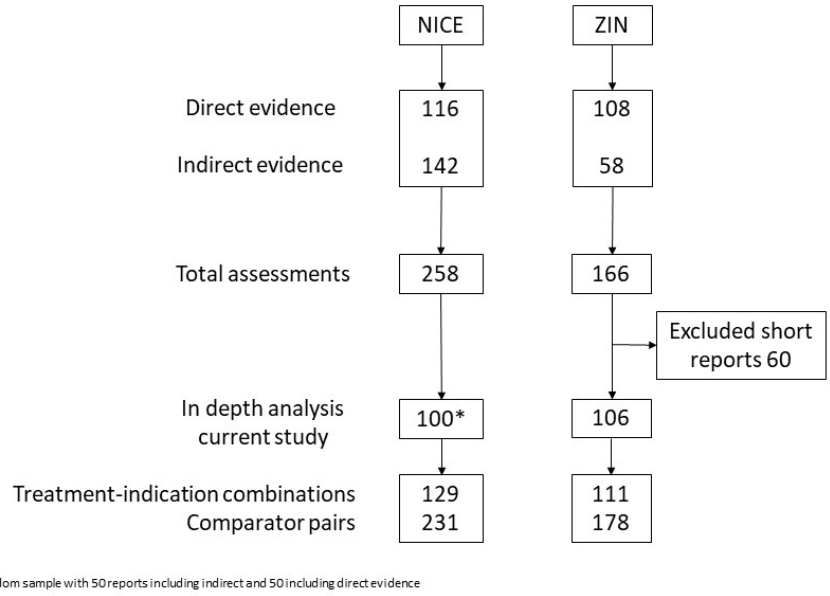

Figure 1. Overview of the number of pharmaceutical reports published between 2015 and 2019 by the National Health Care Institute (ZIN) and the National Institute for Health and Care Excellence (NICE)

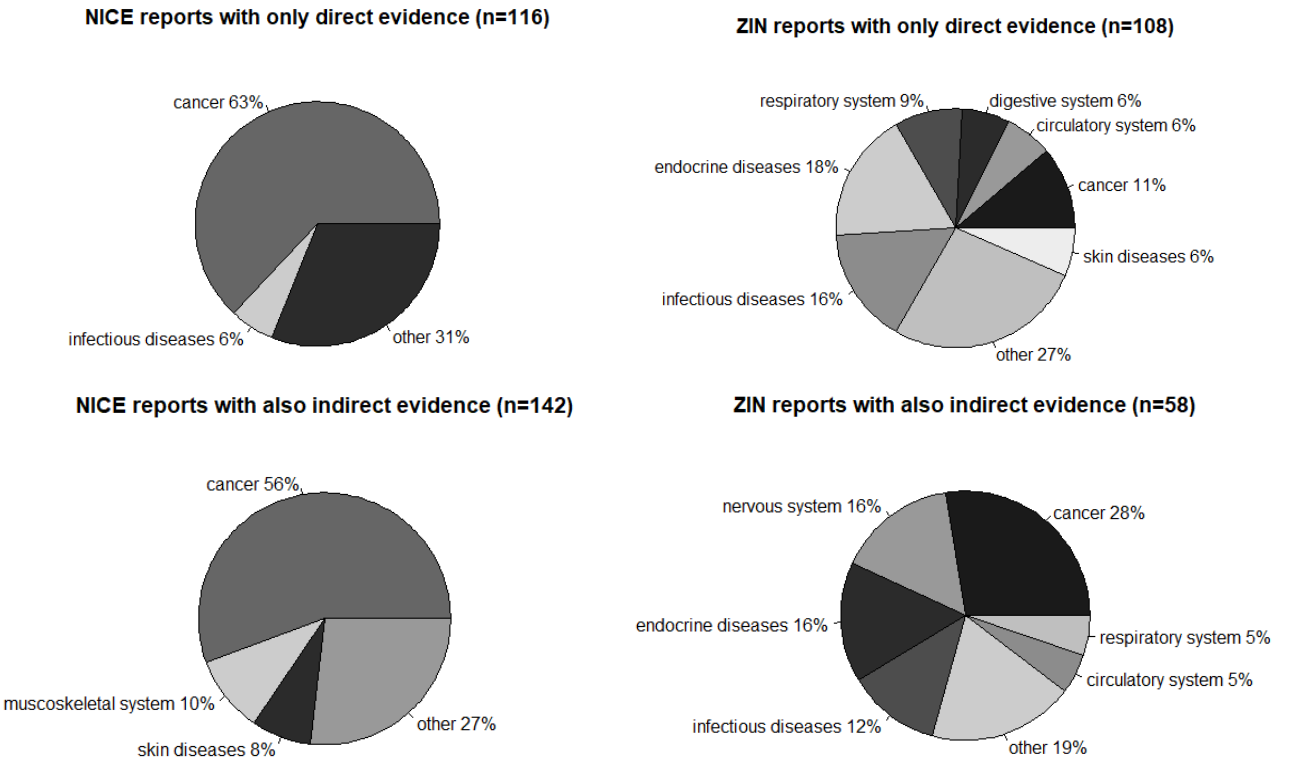

Figure 2. Overview of indications* for which pharmaceutical reports were published by the National Health Care Institute (ZIN) and the National Institute for Health and Care Excellence (NICE) between 2015 and 2019 by the type of evidence used

*Indications for which only a small number of reports (<5% of the total number of reports) were published by ZIN or NICE were combined in the category 'other', this includes for example diseases of the circulatory system and skin diseases.

Table 1. In-depth analysis of REA conclusions and reimbursement recommendations in pharmaceutical reports published between 2015 and 2019 by the National Health Care Institute (ZIN) and the National Institute for Health and Care Excellence (NICE) by type of evidence used

	ZIN (106 reports)		NICE (100 reports)	
	Type of evidence		Type of evidence	
	Direct	Indirect	Direct	Indirect
REA[a]				
Added benefit	40 (58%)	32 (29%)	43 (66%)	87[b] (52%)
Similar benefit	9 (13%)	59 (54%)	16 (25%)	70 (42%)
Lesser benefit	15 (22%)	16 (15%)	2 (3%)	5 (3%)
Other	5 (7%)	2 (2%)	4 (6%)	4 (2%)
Total	69	109	65	166
Reimbursement recommendation[c]				
Positive	25 (42%)	28 (55%)	7 (13%)	29 (40%)
Restricted	16 (27%)	13 (25%)	41 (73%)	31 (42%)
Negative	19 (32%)	10[d] (20%)	8 (14%)	13 (18%)
Total	60	51	56	73

[a] Based on 178 and 231 comparator pairs by ZIN and NICE, respectively
[b] For three comparator pairs the REA conclusions was determined as 'effective' and has been counted as added value.
[c] Based on 111 and 129 treatment-indication combinations by ZIN and NICE, respectively
[d] For one treatment-indication combination no recommendation has been given and has been counted as a negative recommendation.

Table 1 shows the reimbursement recommendations for each of the treatment-indication combinations included. A positive recommendation was given to 42% of the treatment-indication combinations by ZIN when only direct evidence was evaluated, and for 55% when also indirect evidence was evaluated. NICE published a positive recommendation for 13% of treatment-indication combinations including only direct evidence and for 40% when also indirect evidence had been used. A restricted recommendation for treatment-indication combinations was published for 27% and 73% including only direct evidence, and for 25% and 42% including indirect evidence by ZIN and NICE, respectively.

The methods used in ZIN and NICE reports for indirect treatment comparisons are reported in Table 2. In 74% of ZIN treatment-indication combinations a naïve ITC was used when indirect evidence was evaluated, this involves an unadjusted comparison between two studies without any correction for possible confounding. NICE only evaluated naïve ITCs in 10% of the included treatment-indication combinations. In 67% of NICE treatment-indication combinations an NMA was used when indirect evidence had been included, in particular these

were most often Bayesian NMAs. ZIN only assessed an NMA in 8% of treatment-indication combinations.

Table 2. In-depth analysis of type of ITC methods used in treatment-indication combinations from pharmaceutical reports published by the National Health Care Institute (ZIN) and the National Institute for Health and Care Excellence (NICE)

	ZIN (106 reports)	NICE (100 reports)
Naïve ITC	39 (74%)	8 (10%)
Adjusted ITC	5 (9%)	16 (19%)
NMA	4 (8%)	56 (67%)
Unclear	5 (9%)	3 (4%)
Total	53[a]	83[b]

[a] In two assessments two different methods were used, both methods were included
[b] In ten assessments two different methods were used, both methods were included
ITC, indirect treatment comparison; NMA, network meta-analysis; ZIN, National Health Care Institute; NICE, National Institute for Health and Care Excellence

Table 3 provides a few examples of reports published by ZIN and NICE showing the use of direct and/or indirect evidence. In the assessment of tisagenlecleucel-T both ZIN and NICE used the same comparator (salvage chemotherapy) which was based on indirect evidence. Both ZIN and NICE assessed a matching adjusted indirect comparison, NICE also evaluated a naïve ITC. Different outcome measures were used by ZIN and NICE which may have contributed to differences in the recommendation. While ZIN concluded that tisagenlecleucel-T had a decreased therapeutic value compared to salvage chemotherapy and was therefore not recommended, NICE concluded a similar therapeutic value and due to tisagenlecleucel-T not being cost effective recommending it being used within the Cancer Drug Fund.

In the assessment of abemaciclib ZIN and NICE used a different type of indirect comparison (a naïve ITC and an NMA, respectively) although the comparator was the same, also differences in the outcome measures assessed are apparent. In the REA both ZIN and NICE concluded similar benefit. For the assessment of apixaban both ZIN and NICE assessed a direct comparison, however, in addition NICE assessed an indirect comparison due to additional comparators. Both ZIN and NICE concluded based on the direct evidence in the REA that apixaban was of added benefit. Although there are some differences in the assessments of these two treatments the conclusion was the same for both, where ZIN and NICE recommended abemaciclib and apixaban for reimbursement.

Table 3. Examples of pharmaceutical reports from the National Health Care Institute (ZIN) and the National Institute for Health and Care Excellence (NICE) showing the use of direct and/or indirect evidence

Tisagenlecleucel-T (Kymriah) for relapsed or refractory diffuse large B-cell lymphoma Comparator (ZIN and NICE): salvage chemotherapy						
	Type evidence	**Outcome measures direct evidence**	**Outcome measures indirect evidence**	**REA**	**CEA/BIA**	**Reimbursement recommendation**
ZIN	Indirect	N/A	OS, HRQoL, AEs	Decreased value	Not conducted due to decreased value	Not recommended
NICE	Indirect	N/A	Response rate (ORR, CR), OS, PFS	Similar value	Not cost effective	Recommended within the Cancer Drug Fund

Abemaciclib (Verzenios) in combination with an aromatase inhibitor for hormone receptor positive, HER2-negative locally advanced or metastasized breast cancer Comparator (ZIN and NICE): Ribociclib and Palbociclib in combination with a non-steroidal aromatase inhibitor Comparator (NICE): placebo in combination with an aromatase inhibitor						
	Type evidence	**Outcome measures direct evidence**	**Outcome measures indirect evidence**	**REA**	**CEA/BIA**	**Reimbursement recommendation**
ZIN	Indirect	N/A	PFS, AEs, treatment discontinuation due to AEs OS, HRQoL	Similar value	Commercial arrangement	Recommended
NICE	Direct + indirect	PFS, OS, response rate (ORR, DCR, CBR), duration of response, HRQoL, AEs, treatment discontinuation due to AEs	PFS, OS, response rate (ORR, CBR, CR)	Similar value (indirect) and added value (direct)	Commercial arrangement	Recommended

Table 3. Continued

Apixaban (Eliquis) for deep vein thrombosis and pulmonary embolism Comparator (ZIN and NICE): Low-molecular-weight heparin and vitamin K antagonists Comparator (NICE): rivaroxaban, dabigatran etexilate, aspirin Comparator (ZIN): placebo						
	Type evidence	**Outcome measures direct evidence**	**Outcome measures indirect evidence**	**REA**	**CEA/BIA**	**Reimbursement recommendation**
ZIN	**Direct**	Percentage VTE and VTE-related death, percentage fatal and non-fatal lung embolism, percentage deep vein thrombosis, composite outcome of VTE or all cause death, composite outcome of VTE, death due to VTE or death from major bleeding, AEs, percentage recurrent symptomatic VTE all cause death, percentage recurrent VTE-related death, percentage cardiovascular death	N/A	Added value	Not conducted	Recommended
NICE	**Direct + indirect**	Composite outcome of confirmed recurrent symptomatic non-fatal VTE or VTE-related death, composite outcome of confirmed recurrent symptomatic non-fatal VTE or all cause death	number of recurrent VTE or VTE-related deaths, composite outcome of major or clinically relevant non-major bleeding events	Added value (direct) similar value (indirect)	Cost effective	Recommended

ZIN: National Health Care Institute ; NICE: National Institute for Health and Care Excellence ; ITC: Indirect Treatment Comparison; OS Overall Survival; HRQoL Health Related Quality of Life; AEs Adverse Events; N/A Not Applicable; ORR Objective response rate; CR complete response; PFS Progression Free Survival; FVC Forced Vital Capacity; IPF Idiopathic Pulmonary Fibrosis; NMA Network Meta-Analysis; HER2 ; DCR ; CBR ; VTE venous thromboembolism;

Discussion

This study demonstrated that indirect evidence was regularly evaluated in pharmaceutical assessments from ZIN and NICE, namely in 35% and 55% of reports, respectively. An in-depth analysis showed that different methods were employed to include indirect evidence, where ZIN most often evaluated naïve, unadjusted ITCs and NICE most commonly assessed NMAs. The use of indirect evidence had the largest impact on the outcome of the REA, in particular for ZIN the use of indirect evidence seemed to be more commonly associated with similar benefit (54%) compared to the use of only direct evidence (13%). In contrast, the use of indirect evidence did not seem to have a substantial effect on the outcome of the CEA or the final recommendations.

Our study supports previous findings showing that indirect evidence is regularly evaluated by HTA agencies.[18-21] Several studies focused on the acceptability of single-armed trials for reimbursement recommendations[19,21] and showed higher acceptability of such evidence when external comparator data was included[21] exemplifying the importance of using ITCs.

Nevertheless, our study showed differences between ZIN and NICE in the methods employed to evaluate indirect evidence. Both ZIN and NICE provide guidance on the acceptability of ITCs in their HTAs. NICE publishes guidelines specifically tailored to the use and acceptability of indirect evidence,[22-25] while ZIN refers to the ITC guidelines published by the European Network for Health Technology Assessment (EUnetHTA – a platform which facilitates the collaboration between European HTA agencies).[9,26] In these guidelines the importance of choosing a method which is appropriate for the type of indirect evidence available is stressed. More specifically, adjusted ITCs and NMAs are the methods preferred by NICE for indirect evidence as is also shown in our findings. EUnetHTA prefers the use of Bucher's ITC or an NMA, depending on the number of comparators taken into account.[9,26]

Naïve ITCs are specifically mentioned as an inappropriate approach, since these do not preserve randomization. However, in our study ZIN has been shown to mostly evaluate naïve ITCs for reimbursement recommendations, which may in part be due to the evidence submitted by pharmaceutical manufacturers for HTA. In recent years, however, ZIN has been using Bucher's ITC more often which became apparent when discussing this topic with assessors at ZIN (oral communication). Although there are some differences in the acceptability of ITC methods between

ZIN and NICE, research has shown that adjusted ITCs are likely to be accepted by HTA agencies, such as Bayesian NMAs and matching adjusted indirect comparisons (MAIC).[27,28]

Indirect evidence in general was shown to be mostly associated with the outcome similar benefit in the REAs of new pharmaceuticals.[29] This was also shown in our study where ZIN concluded similar benefit in 54% of REA conclusions including indirect evidence. NICE, however, was shown to conclude added benefit more often (e.g. in 52% of REA conclusions including indirect evidence). This difference might be due to NICE basing these REA conclusions on NMAs, instead of on naïve ITCs, leading to less uncertainty regarding the results. Another reason may be the process of HTA used by NICE, where an evidence review group evaluates the evidence submitted by the pharmaceutical manufacturer and may also conduct additional analysis (including ITCs) to complement the evidence for HTA. Finally, the difference in indications evaluated may play a role as well, since NICE evaluated oncology treatments in 59% of reports and ZIN only in 17%. Although we were able to demonstrate the influence of ITCs on REA conclusions, we did not demonstrate any impact of indirect evidence on CEA conclusions. This was not unexpected because many factors play a role in conducting a CEA, and the use of an ITC might only have a relatively small effect on the outcome of the CEA. In addition, the effect of ITCs on the final recommendation was also less pronounced as compared to the REA. This is likely also due to several factors playing a role in HTA reimbursement recommendations, such as price arrangements, stopping rules, or availability for specific subpopulations.

This study has a few limitations. First, although we created an overview of all the pharmaceutical assessments conducted by NICE between 2015 and 2019, we only included a subset for further analysis. Due to the high number of recommendations published by NICE it was not feasible to include them all. By randomly selecting 100 assessments (20 per year), of which 50 included only direct evidence and 50 included also indirect evidence, we somewhat negated this problem. However, it could still lead to bias in our findings. As our results showed, 55% of NICE reports included an ITC, therefore our random sample may oversample reports including only direct evidence. However, we do not expect this to have a large effect on our results. Second, some pharmaceutical assessments were updated after we made our selection of assessments to be included leading to reports being unavailable. For NICE two pharmaceutical assessments have been updated and the reports were unavailable, therefore,

we selected two other assessments for analysis. For ZIN this was not an issue, and all pharmaceutical assessments were available online. Third, we included pharmaceutical assessments until 2019. However, since the recently published revised guidelines of ZIN and NICE do not show many differences regarding indirect evidence as compared to the guidelines we had initially reviewed, we do not expect substantial changes in the acceptability of indirect evidence by these two HTA agencies.[25,30-33]

While direct comparisons will remain to be seen as the gold standard for the REA, the use of indirect evidence will become even more important as the HTAR created by the EU comes into effect.[8] This regulation ensures the long-term sustainability of European HTA collaboration and allows a single EU-level submission for a JCA, which is the equivalent of a REA, of new pharmaceuticals. To ensure all relevant comparators are taken into account in JCAs the use of ITCs will become increasingly important.[34] Nevertheless, several studies have shown differences in the acceptability of indirect evidence by HTA agencies,[4-6] therefore increasing alignment regarding ITCs between European HTA agencies is necessary before the start of the EU HTAR in 2025. In addition, although similar clinical data is used by regulatory bodies for market authorization and HTA agencies for reimbursement decision-making, regulatory bodies seem to be less stringent regarding the evidence requirements than HTA agencies.[28,35] For example, regulatory decisions may be based on single arm studies. When such evidence is subsequently submitted to HTA agencies including an appropriate comparator is important. Consequently, ITC methods may be necessary to bridge the gap between the evidence acceptable for regulatory decision-making and the evidence needed to provide reimbursement recommendations, such as population adjustment methods.[28] It is important to note that such methods are accompanied by an unknown amount of bias, increasing the uncertainty of the relative effectiveness estimates in the REA.[28] As a result recommendations with restrictions may be necessary to minimize the risk of basing reimbursement recommendations on evidence containing great uncertainty.

To conclude, when indirect evidence is evaluated, it may have a substantial impact on the REA conclusion, however the effect on the CEA and final recommendation is difficult to extract since multiple factors play a role. Pharmaceutical assessments including indirect evidence seemed to receive a positive or restricted recommendation in three quarters of recommendations, suggesting evaluation of indirect evidence does not affect the access of new pharmaceuticals in the Netherlands and England. Nevertheless, to ensure that

ITCs are only used in a standardized and qualified way it is important that a greater level of alignment between national HTA agencies is established. Our study showed some differences in the ITC methods acceptable by two HTA agencies, one of which will not be subject to the EU HTAR. However, we expect similar differences to exist between HTA agencies within the EU,[36] warranting increased agreement on acceptable ITC methods, especially considering the upcoming HTAR that will implement EU JCAs that will rely on ITCs.

Authorship Statement

RK designed the study in collaboration with author DDa. RK collected the data together with authors MdV, DDa, CB and EL. RK subsequently analysed the data, and wrote the draft manuscript. All co-authors actively contributed throughout the conduct of the study and critically reviewed and approved the manuscript.

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Appendices

Appendix 1. CEA conclusions in pharmaceutical reports published between 2015 and 2019 by the National Health Care Institute (ZIN) and the National Institute for Health and Care Excellence (NICE) by type of evidence used

	ZIN [a]		NICE [b]	
	Type of evidence		Type of evidence	
	Direct	Indirect	Direct	Indirect
CEA				
Not cost effective	12 (48%)	7 (58%)	13 (23%)	30 (37%)
Cost effective	6 (24%)	2 (17%)	41 (72%)	50 (62%)
Other	7 (28%)	3 (25%)	3 (5%)	1 (1%)
Total	25	12	57[c]	81[d]

[a] ZIN only assesses a CEA when an new pharmaceutical is of added value, therefore only 37 of the 111 treatment-indication combinations included a CEA conclusion and were included in these analysis.

[b] NICE always assesses a CEA, resulting in 129 treatment-indication combinations and were all included in these analysis.

[c] For one treatment-indication combination it was concluded that the treatment was cost effective for a subpopulation, but it was not cost effective in the remaining population. Both conclusions are included in these results

[d] For eight treatment-indication combinations it was concluded that the treatment was cost effective for a subpopulation, but it was not cost effective in the remaining population. Both conclusions are included in these results.

Chapter 8

General discussion

The focus of this thesis was the use of patient-relevant outcome measures in health technology assessment (HTA) reimbursement recommendations and the potential to improve alignment with other stakeholders in the healthcare field. Additionally, it focuses on the importance of developing an evidence ecosystem for HTA. An evidence ecosystem ensures all processes within the ecosystem are aligned with each other, for example by using the same outcome measures.[1] Over the years the importance of patient reported outcomes (PROs) for HTA has become apparent. Especially since new pharmaceuticals may not always improve generally accepted clinical outcome measures, such as survival, but may improve health-related quality of life (HRQoL) or other PROs. Therefore, it has become increasingly critical to select the right outcome measures that are most relevant to patients and can consist of both clinical outcome measures and PROs. The development of an evidence ecosystem allows actors in the healthcare field to work together, understand their commonalities and improve alignment while preserving their institutional responsibilities.[2,3] Benefits of such an ecosystem include limiting the duplication of work and allowing the reuse of the same evidence in multiple settings resulting in increased alignment. Ultimately this may improve access to pharmaceuticals which have a real added value for patients.

Main Findings

The **first research question** that we studied concerned the possible patient relevance of the outcome measures used in regulatory decision-making, HTA recommendations and healthcare quality improvement concerning oncology. As a starting point for assessing patient relevance, we used the International Consortium for Health Outcomes Measurement (ICHOM) standard sets as the gold standard. These standard sets are developed by a group of experts, including clinicians, researchers and patients, to inform (shared) decision-making and quality improvement and contain outcome measures such as overall survival and HRQoL. Of these measures, information on survival, progression, HRQoL, and unfavourable outcomes appear to be important for regulatory decision-making, as well as for HTA recommendations. However, there are differences between regulators, HTA bodies and quality improvement regarding the specific outcome measures (e.g. progression-free survival vs recurrent-free survival) and patient-reported outcome measures (PROMs) used. (Chapter 2 and 3)

The **second research question** focused on the alignment between outcome measures used for regulatory decision-making, HTA recommendations and healthcare quality improvement in the assessment of oncological treatments. In Chapter 2 we showed that both ICHOM and regulators stress the importance of disease-specific outcomes, whereas HTA agencies have a stronger focus on generic outcomes. More specifically, HTA agencies provide generic guidelines, regulatory bodies provide guidelines for oncology in general, and ICHOM provides guidance for specific oncological conditions. It was also demonstrated that intermediate outcomes (such as progression free survival) that were recommended in ICHOM standard sets were more likely to be accepted by regulators than by HTA agencies. Chapter 3 highlights the difference in definitions used for similar health outcomes (e.g. progression free survival versus recurrence free survival) between HTA, quality improvement and ICHOM standard sets. Part A of this thesis concluded that a greater level of alignment is attainable when the ICHOM standard sets are used as guidance for selecting patient-relevant outcome measures throughout the lifecycle of a pharmaceutical.

For the **third research question** we set out to assess the possibilities of social media to contribute to HTA recommendations. Part B demonstrated that a content analysis of social media especially helps to assess the patient perspective, including the identification of adverse events, the identification of patient-relevant HRQoL topics and the effect of medicines on HRQoL. In addition, patient experiences with healthcare (including PROs) can be collected via social media, which is especially useful for patients with rare diseases and who are distributed over wide geographic areas. Chapter 6 showed that social media could help improve the content validity of PROMs, such as HRQoL questionnaires. This is especially important since Chapters 5 and 6 revealed that HRQoL questionnaires contain questions which may not be relevant to patients, and that certain relevant HRQoL topics may be over- or underrepresented in HRQoL questionnaires. One specific topic to keep in mind when administering HRQoL questionnaires was illustrated in Chapter 5 where it became apparent that patients and carers have different perceptions on what they identify as important HRQoL topics. Additionally, certain aspects of HRQoL were also perceived differently by patients in different stages of cancer. Although social media has its merits for HTA, several limitations of its use are apparent. These were highlighted in Chapters 4 and 6, and included validating authenticity, selection and information bias and possible incomplete information on user characteristics.

Finally, the **fourth research question** explored the methods and practices which are currently employed regarding indirect treatment comparisons (ITCs) in HTA recommendations. Part C showed that ITCs were regularly used in the HTAs of pharmaceuticals of the Dutch and English HTA agencies, to ensure all relevant comparators were included. Indirect evidence seemed to have a substantial impact on the relative effectiveness assessment (REA) conclusion, whereas the effect on the cost-effectiveness assessment and the final recommendation is more difficult to determine since multiple factors play a role in their outcome. Indirect evidence seems to be most valuable in REA to determine similar benefit of a new pharmaceutical. Furthermore, pharmaceutical assessments including indirect evidence seemed to receive a positive or restricted recommendation in three quarters of recommendations, suggesting evaluation of indirect evidence does not affect the access of new pharmaceuticals in the Netherlands and England. However, the type of ITC used differed between the Dutch and English HTA agencies, where the Dutch most often evaluated naïve, unadjusted ITCs and the English most commonly assessed NMAs. Similar differences are expected to exist between European HTA agencies, warranting increased alignment on acceptable ITC methods.

In the subsequent sections the main findings will be discussed against the background of the quest for an evidence ecosystem in which outcome measures would be aligned and data could be re-used for multiple purposes: regulation, HTA, clinical decision-making and quality improvement.

Evidence Ecosystem in Healthcare

An evidence ecosystem in healthcare aims to increase the value and decrease the waste in healthcare and research.[1,4] Value may be increased by improving the relevance of evidence collected, since advice based on that evidence (e.g. in systematic reviews, clinical practice guidelines and HTA reports) is not always relevant, often costly, widely duplicated and poorly disseminated.[2,4] Waste may be decreased by reducing the costs, resources and burden of registration in healthcare.[4] To develop such an ecosystem extensive collaboration between the stakeholders involved is required which may prove to be challenging.[1] Nevertheless, when considering pharmaceuticals and other health technologies, an evidence ecosystem is worth striving for. Reimbursement or clinical practice guidelines may need to be adapted because pharmaceuticals may no longer be cost effective due to the arrival of more effective or safer newer pharmaceuticals,

or changes in cost effectiveness because pharmaceuticals run out of patent or because of changes in the price of alternative treatments. Therefore, assessing a pharmaceutical throughout its lifecycle is important for both HTA recommendations and clinical practice. Also regulators have indicated the importance of a lifecycle approach for pharmaceuticals by emphasizing it may improve evidence generation and help to better capture patient preferences.[5] Following a pharmaceutical throughout its lifecycle includes assessing it from development to market access to reimbursement to clinical practice and finally to potential disinvestment.[6] To make this possible the implementation of an evidence ecosystem is important, as is using outcome measures that matter to patients and using instruments that adequately measure these outcomes.

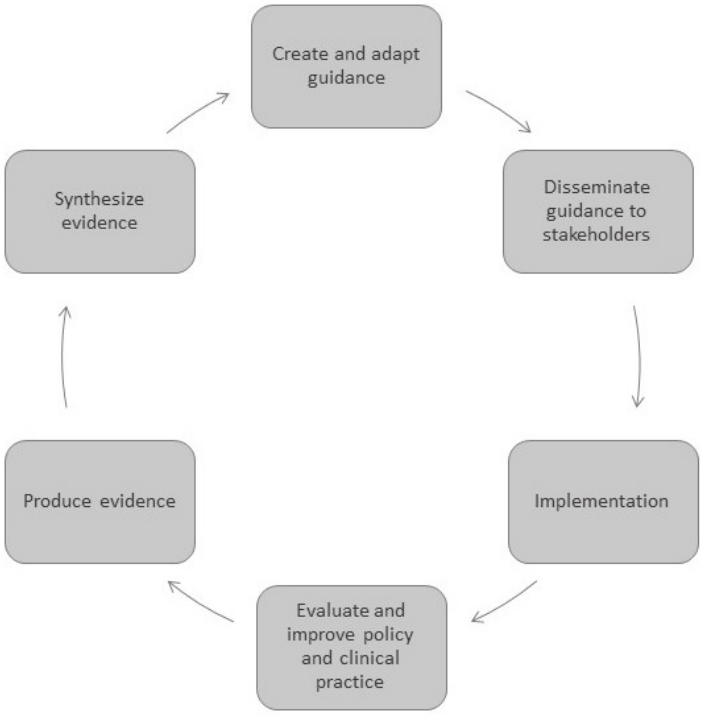

Figure 1. Steps in an evidence ecosystem for healthcare (based on Vandvik and Brandt[1], and MAGIC Evidence Ecosystem Foundation[4])

An evidence ecosystem follows a cyclical approach as is shown in Figure 1.[1,4] Beginning with the **production of evidence** where not only evidence from trials conducted by pharmaceutical manufacturers or universities may be produced, but also real world evidence collected from clinical practice.

Subsequently, this information is **synthesized** in systematic reviews which may then inform the **creation and adaptation** of guidelines, recommendations and reports. Guidance may then be **disseminated to relevant stakeholders**, while ensuring guidance is user friendly and easily understood. For example, the development of decision aids makes this information accessible to patients as will the dissemination of easily understandable HTA reports. Available guidance may be **implemented** by shared decision-making and clinical decision support systems. Finally, **evaluation and improvement of policy and clinical practice** is possible through for example the collection of quality indicators, setting up registries and structurally filling electronic health records. Ultimately, data captured during the evaluation and improvement of policy and clinical practice may feed back into the evidence ecosystem thus creating a virtuous cycle.[1] Within this thesis the focus was on the links 'producing evidence', 'synthesizing evidence', and 'creating and adapting guidance' of the evidence ecosystem. These will be further discussed and related to the main findings of this thesis in the sections below.

Evidence Ecosystem: Producing and Synthesizing Evidence

One aspect which is common for synthesizing evidence – regardless of whether this is done by regulators, in HTA or by clinical guideline developers – is the formulation of the population, intervention, comparison, and outcomes (PICO).[2] Early multistakeholder dialogue and early scientific advice could be used to reach some level of agreement on the PICO necessary to allow each stakeholder to still fulfil their specific purpose.[3] Although there may be some differences in the formulation, e.g. the population may be broader or a different comparator may be preferred, this may be a way to align the different processes as far as the different remits of the various stakeholders allow. One specific aspect of the PICO where agreement may be possible is the use of the same outcome measures and agreeing on definitions and measurements used (e.g. PROMs).[2]

Core outcome sets may help further align and improve patient relevance of accepted outcome measures

Currently many initiatives in clinical healthcare practice exist which are developing core outcome sets, including both clinical outcome measures and PROMs, for shared decision-making and healthcare quality improvement. This includes both international (e.g. ICHOM, OMERACT)[7,8] and national initiatives

(e.g. outcome based healthcare – UGZ)[9] that focus on ensuring outcomes are meaningful, reliable, and easily available. Considering the need for an evidence ecosystem it may be sensible to search for similar outcome measures for regulatory decision-making and HTA recommendations. This may ensure that outcomes and claims based on evidence from RCTs during market authorization and reimbursement could subsequently be substantiated by real-world evidence collected in clinical practice.

Early dialogues between regulators, HTA and clinicians may allow discussions regarding relevant outcome measures for a core outcome set at an earlier stage,[3] ensuring alignment between the different actors in the healthcare field. Including patient organisations in these discussions will help in choosing outcome measures which matter to patients. Agreement on a specific core outcome set allows data collection of the same outcome measures throughout the lifecycle of a pharmaceutical, subsequently reducing duplication of efforts and possibly improving the sharing of information.[10] Hogervorst et al. argue that these core outcome sets do not necessarily need to contain a precisely aligned minimal data set, but should rather be inclusive to ensure all relevant information for each of the actors will be collected.[3] However, the authors also recognize that this may lead to an extensive list of outcome measures. This, in turn, may increase the burden of registration, especially when evidence is collected in clinical practice. A study in the Netherlands showed that healthcare professionals on average spend 52 minutes per day on quality registrations, yet they perceive only 36% of quality indicators to be useful for quality improvement.[11] Although half of the quality indicators were registered for more than one stakeholder, differences between the timing and operationalization of indicators were evident.[11] Administrative burden among healthcare professionals has also been recognized in the United States where the American College of Physicians has published a framework to evaluate existing and new administrative tasks.[12] Therefore, to limit the burden of registration for healthcare professionals it is important to ensure information which is registered in clinical practice is relevant to the different actors in healthcare and alignment between these actors is increased. Nevertheless, some differences will probably remain due to the different remits of the different stakeholders.

Uptake of a core outcome set may still be hard as it may prove difficult to enforce the use of such a set by any one of the actors within the playing field. Therefore, it is important that mandated sets are developed to ensure uptake.[10] European HTA agencies may be in a position to substantiate such a mandated set, since from 2025 onwards the Health Technology Assessment Regulation (HTAR)

will come into effect.[13] This regulation ensures the long-term sustainability of European HTA collaboration and allows a single EU-level submission for a joint clinical assessment (JCA) of new pharmaceuticals. As a JCA will be conducted on a European level agreement between HTA agencies on relevant outcome measures, comparators, and methods used will be important. As part of the HTAR joint scientific consultations (JSCs) will also be conducted, in which relevant experts such as clinicians and patients will be involved. Including relevant stakeholders (e.g. regulators, clinicians, patient organisations) in the choice of these measures and methods may lead to more alignment, and support the creation of mandated core outcome sets as well as support the development of an evidence ecosystem.

Patient reported outcomes increasingly important

Patient reported outcomes (PROs) are increasingly important in all facets of healthcare, being it for market access, reimbursement, healthcare quality improvement or in clinical practice.[14-16] PROs are able to collect information on how a disease and/or the use of a pharmaceutical affects a persons' life, and may be used as aggregate information to facilitate shared decision-making in clinical practice, to improve quality of healthcare delivered, and to inform policy.[17] PROs are also relevant as individual patient data to inform patients during shared decision-making regarding their individual treatment or to follow them through time. Measuring PROs may be viewed as an essential addition to clinical outcome measures when a new pharmaceutical sets out to ameliorate symptoms, improve functioning or improve HRQoL.[15,16] Incorporating PROs in the evidence requirements is especially important when 1) targeting chronic and disabling conditions which are associated with aging populations,[15] 2) new valuable pharmaceuticals have a limited effect on clinical outcome measures, but do improve patient relevant PROs, 3) data on survival are immature and decisions are based on surrogate outcome measures,[18] or 4) when new pharmaceuticals are associated with increased safety risks.[18]

Although PROs are becoming increasingly relevant for HTA, HTA agencies may provide differing guidance on the use of PROs for reimbursement recommendations.[18] In addition, acceptability of PROs may also differ. Where some HTA agencies may prefer generic HRQoL questionnaires, such as the EQ-5D because it is important for their cost-utility analysis, while others prefer a combination of both a generic and a disease-specific HRQoL questionnaire.[18] Considering the requirement of conducting JCAs on a European level due to the HTAR it is important for HTA agencies to align their guidance and acceptability.

As argued in the previous section, they should preferably also involve regulators, clinicians and patient organisations in their choice of outcome measures including PROs. Regulatory bodies may also accept PROs as part of the evidentiary requirements. When comparing the acceptability and use of PROs and PROMs for regulatory decision-making differences between the EMA and FDA are apparent.[19] However, both regulatory bodies accept generic and disease-specific HRQoL questionnaires.[19] In clinical practice, PROs are being increasingly collected for healthcare quality improvement and to allow shared decision-making.[20] Clinical outcome measures and PROs from clinical practice are generally collected via registries. For example, in the Netherlands the Dutch Institute for Clinical Auditing (DICA) collects data to provide insight into the quality of healthcare in oncology.[21] In recent years DICA has increasingly been collecting data on PROs, showing the increased importance of such data for healthcare quality improvement. Another example is the health outcomes observatory (H2O), an initiative which further develops ICHOM sets and aims to collect patient data on a European scale, making it accessible for multiple stakeholders in the healthcare field.[22]

A challenge in choosing PROMs is the balance between disease-specific and generic PROMs. Disease-specific PROMs are more sensitive to change than generic PROMs and may therefore be more relevant when measuring PROs for specific patient populations or for individual patients.[14,23] However, generic PROMs allow for comparison across patient populations, which is especially important for reimbursement recommendations.[14] A combination of disease-specific and generic PROMs would provide a more holistic view of how patients' conditions affects their lives. ICHOM standard sets usually consist of such a combination. As stated previously, in this thesis ICHOM has been used as the gold standard for patient relevance, because ICHOM standard sets are developed using input from clinicians and patients globally.[24,25] In Chapters 5 and 6 we showed that for melanoma patients HRQoL questionnaires contain questions which may not be relevant to them, and that relevant HRQoL topics may be over- or underrepresented in HRQoL questionnaires. ICHOM does not (yet) have a standard set for melanoma. However, an analysis of the content validity of the ICHOM standard sets for breast cancer, Parkinson's disease, diabetes mellitus and rheumatoid arthritis using patients stories on social media showed similar findings: although there is a great deal of overlap between the topics that patients write about on social media and the domain and items of PROMs in ICHOM standard sets, some questions might be redundant, whereas other topics are underrepresented.[23] Thus, even though ICHOM standard sets

are probably one of the best available global standards for patient relevant outcome measures, content validity can still be improved. Social media may offer a valuable source of doing so, as will be discussed in the next section.

Evidence Ecosystem: Create and Adapt Guidance

Social media complementary to traditional forms of research

Social media is used by a large portion of the public worldwide, in July 2023 this amounted to 60% of the world's population.[26] Social media may be defined as an online platform for individuals to get access to, share and generate content.[27] Several types of social media platforms are available, such as blogs (e.g. X, formerly known as Twitter), social networking sites (e.g. Facebook), and content communities (e.g. YouTube).[28] In 2022 a survey commissioned by the European Parliament showed that Facebook (67%), WhatsApp (61%) and YouTube (56%) were the most used social media platforms by individuals above the age of 15. Instagram was also often used by those aged 15-24 (79%) and 25-39 (59%) years old.[29]

Social media is increasingly used by people with concerns regarding their health, including patients with a specific condition, to access, share and generate health-related content.[27,30] So much so, that it has become an important supplement to traditional forms of media and information seeking.[27,31] Patients may find social media, and each other's stories, especially useful in their search to find information on considerations or concerns they have regarding daily life with a specific condition, such as side effects of treatment or coping strategies.[23,32] Ideally such topics would also be discussed with health professionals. However, issues may not be raised by health professionals, topics may not be discussed due to time constraints during consultation, or patients may simply prefer to discuss specific matters with their peers instead of health professionals. In addition, online communities allow patients to contact their peers, and subsequent access to emotional support, at any time of day making it an easily accessible source.[27]

As was shown in part B of this thesis, health-related content on social media may also inform research as it provides a unique insight into the patient's perspective of life with a specific condition. As such, social media may help in pharmacovigilance by helping to identify adverse events.[33,34] It could assist in the recruitment of research participants,[27] especially those who are hard to reach, and it has been shown to be able to assess treatment patterns of

patients.[35] Social media may also be used to identify HRQoL themes relevant to patients with a specific condition, as well as identify themes which are relevant across conditions.[23,32] Additionally, as many PROMs exist social media, such as blogs, could help in choosing the right PROM for a specific situation which reflects outcomes that matter to patients.[23] This is particularly relevant when considering an evidence ecosystem where core outcome sets preferably include aspects of relevance to patients. More specifically, the content validity of core outcome sets should be evaluated based on the set as a whole rather than the elements of the set separately, which will ensure all relevant aspects are addressed together.[23]

Considering which type of social media platform to select when using it to conduct research is important since many different platforms exist, each with its own merits. Blogs, for example, have been successfully used to identify what patients with a specific condition find important regarding their HRQoL.[23] Health-related forums have been shown to frequently be used for emotional support, to share health-related experiences, and to ask for medical advice.[36] Social networking sites, on the other hand, were frequently used to share health-related news and educational material.[36] However, what users share may differ depending on the topic of interest, for example when discussing the topic headache on social networking sites health-related experiences are frequently discussed, but when considering other health problems experiences may be discussed less frequently.[36] In addition, based on age different social media platforms are used to search for health-related information, where those born between 1997 and 2012 (Gen Z) most often use TikTok, Instagram or X while those born between 1981 and 1996 (Millennials) most often use Facebook, TikTok or X for example.[30] Before using social media for research it is therefore important to at least determine what is the topic(s) of interest, who is the target study population, and how best to reach them.

Although using social media to inform research adds value to the body of evidence, Chapters 4 and 6 of this thesis highlight there are some drawbacks. A few of these drawbacks will be discussed here. First, validating the authenticity of content creators may prove to be difficult as individuals may create fake profiles which subsequently may affect the validity of data from social media.[37,38] Moderators are a way to keep fake profiles from social media platforms, however not every platform makes use of moderators to curate posts. Second, use of social media platforms may result in incomplete information on user characteristics.[38] Third, social media is prone to selection bias as socio-

demographic characteristics of social media users differ across social media platforms, such as age, gender and income.[39,40] In addition, those who use social media may differ from those who do not.[41] For example, British social media users have been shown to be better educated and wealthier than the general British population.[39] Finally, information bias may be an issue as some social media users may be more vocal online than others, for example negative reviews may be underrepresented.[42]

When considering using social media for research purposes it is important to consider the ethical aspects of doing so, such as not linking data to individuals without consent and ensuring anonymity.[37] It has been argued that the same ethical considerations should apply as for traditional research,[37] however, applying new rules has also been proposed.[43] New rules may be relevant, since the boundary between private and public has blurred with the use of social media. Users who generate health information intend for other users to read it and did not intend for it to be used in research, however, by placing information in the public domain control over it is waived.[37,43] In addition, when using social media content for research it is important to determine whether users should be seen as research subjects, in which case informed consent should be obtained, or as authors, in which case they should be acknowledged as such.[43] Ethical considerations are specifically relevant when considering accessibility of social media content, where some content is freely accessible to anyone while other content requires a login.[44] Should user-generated content be part of research when it can only be accessed after logging in? Unfortunately, there is a lack of practice guidelines that address ethical aspects, such as privacy issues, associated with using social media for research.[27]

Yet, it is important to develop such guidance, because information (collected) on social media may provide actors in healthcare, including regulators, HTA agencies and clinicians, with a more holistic understanding of the factors affecting patients' HRQoL, especially when new pharmaceuticals have a limited added value regarding clinical outcome measures (e.g. survival). Since, as mentioned before, benefits of a new treatment may also be expressed in terms of improving symptoms, functioning or HRQoL which can be measured using PROMs. Social media provides a potential source of real-world data to help better understand disease burden and unmet clinical need.[35] Patient stories available on social media may enable stakeholders in the healthcare field to gain a broad and in-depth understanding of what patients experience when living with their condition.[32] However, considering the limitations of using social media for

research (e.g. fake profiles, selection bias) and the objective of the study, social media may be best used complementary to traditional forms of research.

Indirect Treatment Comparisons make it possible to include direct and indirect evidence

Even when there is agreement in outcome measures between the different actors in the evidence ecosystem there may still be some differences to allow each of those actors to pursue their purpose. One specific difference is the use of different comparators between regulators and HTA, but also between national HTA agencies. In addition, it seems that fewer randomized trials are being conducted and more observational and real world data are being submitted.[45] Incorporating such data in the assessment process using the right methods is important.[45,46] Mixed treatment comparisons (such as Network Meta Analysis – NMAs) allow the comparison of both direct and indirect evidence and could incorporate observational and real world data.[47] Not only are methods for ITCs continuously being improved and developed, also software to easily conduct ITCs have been developed. For example, within the IMI-GetReal Initiative the ADDIS tool has been developed which is a data management and analytical tool which allows users to conduct NMAs and benefit-risk analysis.[48,49] Such methods not only allow for comparisons when different comparators have been used, they also allow taking all the evidence being collected throughout the lifecycle of a pharmaceutical into account. This ensures that not only RCT data, but also real-world data collected in clinical practice may be incorporated allowing to bridge the gap between efficacy (regulatory decision-making) and effectiveness (HTA recommendations).[47] Indirect treatment comparisons (ITCs) may also be relevant for clinicians to compare the different treatment options considered for a specific patient. Nonetheless, ITCs can only be conducted when the same outcome measures have been used in the different sources of evidence (e.g. RCT data, real-world evidence), thus, further showing the importance of alignment between the different healthcare actors.

Limitations

For the studies presented in this thesis several limitations and challenges should be addressed.

Firstly, we did not to include all European HTA agencies in our research. Since HTA is conducted on a national level each European country has its own HTA agency. In

our research we mainly focused on the Dutch (Chapters 2, 3, 7), English (Chapters 2, 3, 7) and German (Chapter 2) HTA agencies. Although this is a small sample of European HTA agencies we believe this provides a valid start for assessing the alignment between regulatory decision-making, HTA recommendations and healthcare quality improvement, as well as provide an indication regarding the acceptability and use of ITCs for reimbursement recommendations. In Chapter 2 we also included the guidelines from the European Network for Health Technology Assessment (EUnetHTA), since it facilitates collaboration between European HTA agencies. In doing so, EUnetHTA guidelines provide a European viewpoint.

Secondly, when comparing outcome measures used by regulators, HTA and for healthcare quality improvement we based our study on comparison of reports. The inclusion of questionnaires and/or interviews with relevant stakeholders would have added additional insights.

Thirdly, within this thesis the ICHOM standard sets were taken as the gold standard for patient-relevance. However, many other core outcome sets are available as is evident from the number of sets published on the Core Outcome Measures in Effectiveness Trials (COMET) website, such as OMERACT.[8] ICHOM has developed multiple sets for differing conditions and used a similar approach for each set,[24] therefore, suggesting the sets are comparable. However, including patient perspectives using questionnaires and/or interviews would have provided further detail to our results.

Lastly, we mainly focused on oncology, therefore, results may be different when assessing other conditions. However, oncology is a field in which many new pharmaceuticals are being developed and often for small patient populations. It may therefore provide an adequate overview of methods and outcome measures used and accepted by regulators, HTA agencies, clinicians and for quality improvement.

Future Research

Based on this thesis, several recommendations can be made regarding future research.

Further efforts from all healthcare stakeholders is necessary to further implement an evidence ecosystem. Future research should focus on the

common grounds between the different stakeholders and the aspects needed to implement this ecosystem while keeping the purpose of each of the stakeholders in mind to ensure they can comply with their intended purpose. This is not only a substantive problem (which outcome measures are relevant for all actors?) but also a governance issue (who has the power to mandate what is being measured 'upstream'? Who will ensure that the patient's voice is being heard in this process? And how?).

As mentioned in this thesis both clinical outcome measures and PROs are relevant to inform an evidence ecosystem. Clinical outcome measures have been collected on a regular basis in both randomized controlled trials and clinical practice. PROMs however, have proven to be more difficult to implement, as PROM completion rates tend to be low.[14] Especially implementation of routinely collecting PROMs in clinical practice may be a focus for future research.

Finally, in 2025 the HTAR will come into effect in Europe. It will be important to evaluate whether this will actually increase alignment and subsequently efficiency[10] by reducing duplication and increasing manpower for evaluating new pharmaceuticals. In addition, it will also be important to evaluate how pharmaceutical manufacturers experience a REA submission on a European level. Ultimately future research should focus on whether patient access to new valuable pharmaceuticals in a timely fashion has improved due to the HTAR.

Recommendations for Practice and Policy

Several recommendations can be made regarding an evidence ecosystem for healthcare:

- Regulatory bodies, HTA agencies and clinicians should aim to increase alignment in the definitions of outcome measures used. Additionally, making use of the same outcome measures should be preferred when appropriate. However, the different remits of each of the stakeholders may not always allow alignment,[2] in such instances inclusion of all relevant outcome measures may be more appropriate.[6] Increasing understanding of these different remits is important to ensure collaboration between the different stakeholders. To do so, communication between the actors must be improved, for example early dialogues and horizon scanning could contribute.[6]

- An evidence ecosystem is based on the premise that outcome measures are available for all stakeholders within that ecosystem. However, this may not always be the case. To ensure data collected in clinical practice, for instance in registries, may be used for other processes in the ecosystem a culture of sharing data amongst stakeholders is pertinent.[1] Otherwise an evidence ecosystem will fail to work. To support the sharing of health data, the European Commission has presented a regulation to set up the European Health Data Space (EHDS).[50] This regulation is envisioned to promote the reuse of health data for research, innovation, policy-making and regulatory activities.[50] However, some concerns need to be overcome in order for the EHDS to be implemented successfully.[51,52] These include but are not limited to, overcoming differences in the quality of health data in Europe and tackling the diverging interpretations of EU data protection rules by EU Member States.[51,52]

Several policy recommendations can be made:

- National HTA agencies should continue to work on their collaboration. Since 2006 EUnetHTA has supported collaboration of European HTA agencies by developing guidelines and enabling joint relative effectiveness assessments.[53] However, as the HTAR will be introduced in 2025 this will require further collaboration between national HTA agencies as joint clinical assessments will become necessary.[10]

- The importance of involving patient organisations during the HTA process has been widely recognized,[54,55] nevertheless, including patient input may prove to be difficult.[55,56] For example, despite having policies in place for patient involvement during the HTA process, due to time constraints the Dutch National Health Care Institute hardly involved patients during the scoping phase or when defining relevant outcome measures in pharmaceutical assessments conducted in 2019.[57] Since implementing patient involvement in HTA processes may still prove to be difficult, data from social media may provide a solution as it gives insight into the patient perspective. This input may be of value during the scoping phase of an HTA or to inform topic prioritization.

- In the evaluation of ITCs for regulatory decision-making, HTA recommendations and clinical practice it is important to ensure correct methods are used for the data available.[45,46] In addition, the acceptability of such methods by the different actors in the healthcare field should be clear. The EUnetHTA and EU

HTAR guidelines may be a starting point regarding the methods to be used and accepted.[58,59]

- Although the relevance of collecting PRO(M)s for regulatory decision-making, HTA reimbursement recommendations, clinical care and quality improvement is evident,[16,20] implementing PROM collection in clinical practice remains difficult. To allow the systematic collection of standardized PROs adequate, secure and interoperable systems are important.[60]

Conclusion

The studies in this thesis have demonstrated that outcome measures used for reimbursement recommendations are patient relevant. However, there is still room for improvement. Social media may identify additional aspects that affect a patient's HRQoL and provide regulators, HTA agencies and clinicians with a more holistic view of what matters to patients. In addition, this type of information may support the scoping phase before the value assessment of new health technologies and inform topic prioritization.

We have also shown that there already is some alignment in outcome measures used between the different actors in the healthcare field, more specifically between regulatory bodies, HTA agencies and healthcare professionals (i.e. quality improvement). Nevertheless, additional alignment may be possible by using the same definitions for outcome measures and requiring the same PROMs. Alignment may not always be preferred or possible considering the different remits of each of the stakeholders, therefore, it may be relevant to be more inclusive regarding outcome measures rather than aim for minimum datasets. In addition, when different comparators are preferred or when different types of evidence (e.g. data from RCTs, real world data) are available ITCs may be a solution that tackle such methodological issues. However, this is only possible when outcomes are standardized underlining the importance of creating a common language for measuring outcomes throughout the evidence ecosystem.

Authorship Statement

RK wrote the discussion, while her supervisory team provided feedback during the whole process. RK implemented this feedback and her supervisory team approved the final version.

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Appendices

Summary

Introduction

To support sustainable healthcare while ensuring patients access to pharmaceuticals with an added value it is important to adequately measure health outcomes resulting from treatment with these pharmaceuticals. An evidence ecosystem may support monitoring of pharmaceuticals through its lifecycle, from early clinical trials through market authorization and from reimbursement to subsequent appropriate use in clinical practice. However, to implement such an evidence ecosystem and allow evaluation of the use of a pharmaceutical throughout its lifecycle it is important that health outcomes that are measured are similar over the lifecycle within the evidence ecosystem. In addition, methods which allow for the coherent analysis of all available evidence on those treatments is important. As an evidence ecosystem consists of multiple actors this thesis takes health technology assessment (HTA) agencies as a starting point. HTA agencies are responsible for providing healthcare payers with reimbursement recommendations which allows for the identification of pharmaceuticals and other health technologies which offer the best value for money. The focus of this thesis was the use of patient-relevant outcome measures in health technology assessment (HTA) reimbursement recommendations and the potential to improve alignment with other stakeholders in the healthcare field.

Patient relevance of health outcome measures used in regulatory decision-making, health technology assessment recommendations and quality of healthcare

In **Part A** of this thesis the overlap between health outcome measures used for regulatory decision-making, HTA reimbursement recommendations, and quality of health care are explored and compared to outcome measures which are deemed to be relevant to patients. As a starting point for assessing patient relevance, the International Consortium for Health Outcomes Measurement (ICHOM) standard sets were used as the gold standard.

In **Chapter 2** we studied the extent to which health outcome measures used by regulators and HTA agencies are patient relevant by comparing these to ICHOM standard sets. Two regulators were assessed, namely the European Medicines Agency (EMA) in Europe and the Food and Drug Administration (FDA) in the United States. Three HTA agencies were selected, namely the National Health Care Institute (ZIN) in the Netherlands, the National Institute for Health and Care Excellence (NICE) in England, and the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany. We conducted a cross-sectional comparative analysis of ICHOM standard sets and publicly available regulatory

and HTA guidelines, with a focus on oncology. We showed that overall similar outcomes (such as survival, morbidity and safety estimates) are relevant for market access and reimbursement, and are included in ICHOM standard sets. However, some differences remain, such as the acceptability of intermediate outcomes. These are recommended in ICHOM standard sets, but regulators are more likely to accept intermediate outcomes than HTA agencies. In addition, ICHOM and regulators stress the importance of disease-specific outcomes, while HTA agencies have a stronger focus on generic outcomes. It was concluded that a greater level of alignment in evidence requirements regarding health outcomes may enhance the efficiency of regulatory and HTA processes and increase timely access to new medicines with additional value. ICHOM standard sets may help align these outcome requirements.

In **Chapter 3** we evaluated the agreement in outcome measures used in oncology for healthcare quality improvement and HTAs, and aligned those to ICHOM standard sets again. We conducted a cross-sectional comparative analysis of ICHOM sets focusing on oncological indications, and publicly available measures for healthcare quality and HTA reports published by the Dutch National Health Care Institute (ZIN) and the English National Institute for Health and Care Excellence (NICE). Information on overall survival, disease progression, health related quality of life (HRQoL) and unfavourable outcomes seem to be important for both HTA and quality improvement, although there are differences in the specific outcome measures used. These domains are also incorporated in ICHOM standard sets. Although for HTA and quality improvement as well as in ICHOM sets outcome measures are used from the same domains, a greater level of alignment seems possible by using the same definitions for similar health outcomes (e.g. progression free survival versus recurrence free survival). ICHOM may provide input on standardized outcome measures to support this alignment.

Part A concluded that a greater level of alignment on health outcome measures being used is attainable between the different actors in the healthcare field when the ICHOM standard sets are used as guidance for selecting patient-relevant outcome measures throughout the lifecycle of a pharmaceutical. However, residual discrepancies will remain due to the different remits of each of the actors.

Possibilities of social media to contribute to health technology assessment recommendations

New pharmaceuticals may sometimes demonstrate limited added benefit based on the clinical outcomes that are measured. However, these pharmaceuticals may

improve health related quality of life (HRQoL) of patients, which can be measured by patient reported outcomes (PROs). For that reason the measurement of PROs has become increasingly important for market authorization and reimbursement recommendations. Unfortunately, PROs are often not systematically collected and are not always submitted by pharmaceutical manufacturers for regulatory or HTA evaluations. In addition to the limited availability of HRQoL data, current methods used to measure HRQoL may fail to truly capture what is most relevant to patients. Therefore, there is a continuous search for sources that provide additional information on HRQoL. Social media is a convenient and well-established communication source, and may be a potential option for information regarding PROs, such as HRQoL. Therefore **Part B** explored how information derived from social media could provide additional input for HTA reports that support reimbursement recommendations.

The aim of **Chapter 4** was to assess the extent to which health data generated from social media may provide insights for HTA. We conducted an explorative literature review to identify examples in oncology where health data were collected using social media. Scientific and grey literature published between January 2010 and June 2016 was identified by four reviewers, who independently screened studies for eligibility and extracted data. A descriptive qualitative analysis was performed. Of 1032 articles identified, eight were included: four articles identified adverse events in response to cancer treatment, three articles disseminated quality of life (QoL) surveys, and one study assessed the occurrence of disease-specific symptoms. Several strengths of social media-generated health data were highlighted in the included literature, such as efficient collection of patient experiences and recruitment of patients with rare diseases. Conversely, limitations included validation of authenticity and presence of information and selection bias. This study showed that social media may provide a potential source of information for HTA, particularly on aspects such as adverse events, symptom occurrence, HRQoL, and adherence behaviour.

In **Chapter 5** we focused on the feasibility of using social media to collect melanoma patients' perspectives on HRQoL, and whether currently established cancer- and melanoma-specific HRQoL questionnaires really represent melanoma patients' perspectives. A survey was distributed on the social media channels of Melanoma Patient Network Europe. Two researchers independently conducted content analysis to identify key themes, which were subsequently compared to questions from one current cancer-specific and two melanoma-specific HRQoL questionnaires (i.e. EORTC QLQ-C30, EORTC QLQ-MEL38, FACT-M). Our

analysis showed that patients indicated good *family relationships*, *having a normal life*, and *enjoying life* as the three most important aspects of HRQoL. Carers for those patients indicated that according to their perspectives being capable of doing daily tasks, having manageable adverse events, and being pain-free were the three most important aspects of HRQoL for patients. Both patients and carers seem to find some questions from HRQoL questionnaires relevant (e.g. 'Have you felt able to carry on with things as normal?') and others less relevant (e.g. 'Have you had swelling near your melanoma site?'). Additionally, wording may differ, where patients and carers generally use a more positive tone than questions in HRQoL questionnaires. Our study suggests that cancer- and melanoma- specific HRQoL questionnaires currently available do not seem to fully reflect what patients view as important in HRQoL, particularly in relation to wording of issues. This raises the question of whether information generated from current cancer- and melanoma-specific HRQoL questionnaires should be used for HTA decision-making or if alternatively new, patient-centred, stage-specific instruments should be developed that better reflect patient perspectives on HRQoL.

In **Chapter 6** we identified the HRQoL topics important to melanoma patients based on web-based discussions on public social media forums. Posts were randomly selected from 3 public web-based oncology forums from the United States and the United Kingdom. Posts were coded using qualitative methods until saturation was reached. In this study, we showed that topics related to *fear*, *worry and anxiety*, *uncertainty*, and *unfavourable effects* were most often discussed between patients. We concluded that web-based forums are a valuable source for identifying relevant HRQoL aspects in patients with melanoma. These aspects could be cross-referenced with existing tools and might improve the content validity of patient-reported outcome measures, including HRQoL questionnaires. In addition, web-based forums may support HTA agencies during topic prioritization as well as during the scoping phase conducted before the value assessment of a new health technology.

Part B showed that social media is a readily available source of information that can provide fast input on HRQoL from patients with both rare and common diseases. It can be used to listen to what patients discuss on the web and to distribute questionnaires. In addition, information extracted from social media may support an evidence ecosystem, where existing evidence is used by several stakeholders for different goals. This information source may contribute to a more holistic understanding of the patient's perspective and highlight issues

affecting patients HRQoL. However, health data from social media is prone to selection and information bias, and validating authenticity can be difficult. Therefore, this type of data should be used complementary to traditional forms of research.

Potential of indirect treatment comparisons for health technology recommendations

Part C discusses the potential of using indirect treatment comparisons (ITCs) for HTA.

The aim of **Chapter 7** was to evaluate the acceptability of ITCs in HTA in the Netherlands and England and to evaluate whether there was a relationship between the outcome of the relative effectiveness assessment, cost effectiveness assessment and reimbursement recommendation, and the use and outcome of ITCs. Initially all HTA reports on pharmaceuticals published between 2015 and 2019 by the Dutch National Health Care Institute (ZIN) and English National Institute for Health and Care Excellence (NICE) were included. Subsequently, for in-depth analysis all full reports of ZIN were included while for NICE 100 reports (random sample; 20 per year) were included. Analysis of ZIN and NICE reports showed that ITCs are very common. Indirect evidence may have a substantial impact on the conclusion of the relative effectiveness assessment, however the effect on the cost effectiveness assessment and final recommendation is difficult to extract since multiple factors play a role. Pharmaceutical assessments including indirect evidence seemed to receive a positive or restricted recommendation in three quarters of recommendations, suggesting that evaluation of indirect evidence does not have a pronounced negative impact on the access of new pharmaceuticals in the Netherlands and England. The ITC methods used differed between the two agencies which may depend on the type of pharmaceuticals assessed but also on their assessment process. Our results support a further alignment of the process and methods of ITCs used by national HTA agencies, especially considering the foreseen EU HTA regulation which ensures consistent comparative evaluation of new pharmaceuticals within Europe.

General Discussion

In **Chapter 8** we summarized the main findings and put these into a broader perspective with recommendations for future research, and for practice and policy.

Recommendation for future research:

- Focus on the common grounds between the different stakeholders and the aspects needed to implement an evidence ecosystem while keeping the remits of each of the stakeholders in mind to ensure they can comply with their intended purpose.
- Further implementation of routinely collecting PROMs in clinical practice may be a focus for future research.
- Focus on how ITCs are implemented and evaluated in joint clinical assessments when the EU HTA Regulation (HTAR) comes into effect in 2025.

Recommendations for practice and policy:

- Increased alignment in definitions and use of outcome measures between regulatory bodies, HTA agencies and clinicians, while also increasing understanding of the different remits of each of the stakeholders.
- Encourage a culture of sharing data amongst stakeholders, to ensure data collected in clinical practice, for instance in registries, may be used for other processes in the evidence ecosystem.
- National HTA agencies should continue to work on their collaboration to ensure that when an evidence ecosystem is developed and implemented it will be of added value on both a national and international level.
- Increase the incorporation of patient perspectives during the HTA process to inform the scoping phase of an HTA or to inform topic prioritization, for example by involving patient organizations or by using information from social media.
- Define acceptable methods for ITCs for regulatory decision-making, HTA recommendations and clinical practice to allow the development of an evidence ecosystem. These methods should be included as part of the new methodological guidelines that are developed as part of the process on the joint clinical assessments under the EU HTA Regulation.
- Increase the systematic collection of standardized PROMs using secure and interoperable systems ensuring the availability of such data for all the actors within the healthcare field.

To conclude, the studies in this thesis suggest that outcome measures used for reimbursement recommendations are mostly patient relevant. However, patient perspectives could be included more often during the scoping phase or for topic prioritization. Social media could provide such input. This thesis also showed that there is already some alignment in outcome measures used between the different actors in the healthcare field. Additional alignment may be possible, but may not always be preferred due to the different remits of each of the stakeholders. If similar outcomes are being used indirect comparisons, based on common and agreed methodology, may facilitate relevant comparisons between different treatments in various settings. However, this is only possible when outcomes are standardized underlining the importance of creating a common language for measuring outcomes throughout the evidence ecosystem.

Samenvatting

Introductie

Om ervoor te zorgen dat de gezondheidszorg betaalbaar blijft en patiënten toegang behouden tot geneesmiddelen met een toegevoegde waarde is het van belang om het effect van deze geneesmiddelen met de juiste en adequate gezondheidsuitkomsten te meten. Een ecosysteem voor bewijs in de gezondheidszorg (*evidence ecosystem)* kan ondersteuning bieden bij het monitoren van deze geneesmiddelen over de gehele levenscyclus, van vroeg klinisch onderzoek tot markttoelating en van vergoeding tot het gebruik in de klinische praktijk. Om een dergelijk *evidence ecosystem* te ontwikkelen en implementeren voor de evaluatie van geneesmiddelen is het echter van belang dat dezelfde gezondheidsuitkomsten gemeten worden gedurende de levenscyclus van een geneesmiddel. Bovendien zijn methoden die een coherente analyse van al het beschikbare bewijs over deze uitkomsten mogelijk maken belangrijk. Aangezien binnen een *evidence ecosystem* meerdere actoren actief zijn, neemt dit proefschrift *health technology assessment* (HTA) instanties als uitgangspunt. HTA instanties zijn verantwoordelijk voor het doen van aanbevelingen over vergoeding aan de betalende partijen (zoals overheden en verzekeraars) van gezondheidszorg. HTA maakt het mogelijk om geneesmiddelen en andere gezondheidstechnologieën te identificeren die de beste waarde voor geld bieden. De focus van dit proefschrift ligt op het gebruik van gezondheidsuitkomsten die relevant zijn voor patiënten in HTA beoordelingen en de potentie om de afstemming met andere actoren over deze uitkomsten in het gezondheidszorgveld te verbeteren.

Patiëntrelevantie van gezondheidsuitkomsten die worden gebruikt bij markttoelating, vergoedingsbeoordelingen en kwaliteit van gezondheidszorg

In **Deel A** van dit proefschrift wordt de overlap onderzocht tussen gezondheidsuitkomsten die worden gebruikt voor markttoelating, vergoedingsbeoordelingen en de kwaliteit van de gezondheidszorg. Vervolgens worden deze gezondheidsuitkomsten vergeleken met uitkomsten die worden beschouwd als relevant voor patiënten. Als startpunt voor het beoordelen van patiëntrelevantie werden de standaardsets van het *International Consortium for Health Outcomes Measurement* (ICHOM) gebruikt als de gouden standaard.

In **Hoofdstuk 2** hebben we de mate waarin gezondheidsuitkomsten die worden gebruikt voor markttoelating en vergoedingsbeoordelingen patiëntrelevant zijn bestudeerd door deze te vergelijken met de standaardsets van ICHOM. Twee regulerende instanties zijn beoordeeld, namelijk het *European Medicines*

Agency (EMA) in Europa en de *Food and Drug Administration* (FDA) in de Verenigde Staten. Drie HTA instanties werden geselecteerd, namelijk het Zorginstituut Nederland (ZIN) in Nederland, het *National Institute for Health and Care Excellence* (NICE) in Engeland en het *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (IQWiG) in Duitsland. We hebben een vergelijkende analyse uitgevoerd van ICHOM standaardsets en publiek beschikbare richtlijnen van regulerende en HTA instanties. Hierbij lag de focus op oncologie. We hebben aangetoond dat over het algemeen vergelijkbare uitkomsten (zoals overleving, morbiditeit en bijwerkingen) relevant zijn voor markttoelating en vergoedingsbeoordelingen, deze zijn ook opgenomen in ICHOM standaardsets. Er blijven echter enkele verschillen bestaan, zoals de aanvaardbaarheid van intermediaire uitkomsten. Deze worden aanbevolen in ICHOM standaardsets, maar regulerende instanties zijn eerder geneigd intermediaire uitkomsten te accepteren dan HTA instanties. Daarnaast benadrukken ICHOM en regulerende instanties het belang van ziektespecifieke uitkomsten, terwijl HTA instanties een sterkere focus hebben op generieke uitkomsten. Er werd geconcludeerd dat een grotere mate van afstemming over het vereiste bewijs de efficiëntie van regulerende en HTA processen kan verbeteren en de tijdige toegang tot nieuwe geneesmiddelen met toegevoegde waarde kan vergroten. ICHOM standaardsets kunnen helpen bij het afstemmen hiervan.

In **Hoofdstuk 3** hebben we de overlap in gezondheidsuitkomsten geëvalueerd die worden gebruikt in de oncologie voor verbetering van de kwaliteit van de gezondheidszorg en de HTA beoordelingen, deze hebben we opnieuw afgezet tegen de ICHOM standaardsets. We hebben een vergelijkende analyse uitgevoerd van ICHOM sets gericht op oncologische indicaties, en openbaar beschikbare informatie over uitkomsten gebruikt voor het meten van de kwaliteit van de gezondheidszorg alsook HTA rapporten gepubliceerd door het Nederlandse ZIN en het Engelse NICE. Informatie over algehele overleving, ziekteprogressie, gezondheidsgerelateerde kwaliteit van leven (HRQoL) en ongunstige uitkomsten lijken belangrijk te zijn voor zowel HTA als kwaliteitsverbetering, hoewel er verschillen zijn in de definitie van de gebruikte gezondheidsuitkomsten. Deze domeinen zijn ook opgenomen in de geïncludeerde ICHOM standaardsets. Hoewel voor HTA en kwaliteitsverbetering, evenals in ICHOM sets, uitkomstmaten worden gebruikt uit dezelfde domeinen, lijkt een grotere mate van afstemming mogelijk door dezelfde definities te gebruiken voor vergelijkbare gezondheidsuitkomsten (bijv. progressievrije overleving versus recidiefvrije overleving). ICHOM kan bijdragen aan het standaardiseren van deze gezondheidsuitkomsten om afstemming te ondersteunen.

In **deel A** concluderen we dat een grotere mate van afstemming omtrent gezondheidsuitkomsten haalbaar is tussen de verschillende actoren in het gezondheidszorgveld. Hierbij kunnen de ICHOM standaardsets worden gebruikt als richtlijn voor het selecteren van patiëntrelevante gezondheidsuitkomsten. Er zullen echter verschillen blijven bestaan tussen de actoren vanwege hun verschillende taken en doelen. Desalniettemin is het van belang om duidelijke afspraken te maken over de gezondheidsuitkomsten die gedurende de levenscyclus van een geneesmiddel gemonitord dienen te worden.

Mogelijkheden van sociale media om bij te dragen aan HTA beoordelingen

Nieuwe geneesmiddelen kunnen soms een beperkt voordeel tonen op basis van de klinische uitkomsten die worden gemeten. Deze geneesmiddelen kunnen echter wel de kwaliteit van leven van patiënten verbeteren, wat gemeten kan worden aan de hand van patiënt gerapporteerde uitkomsten (PRO's). Het gebruik van PRO's is dan ook steeds belangrijker geworden voor markttoelating en vergoedingsbeoordelingen. Helaas worden PRO's vaak niet systematisch verzameld en worden ze niet altijd ingediend door fabrikanten voor regulerende of HTA beoordelingen. Naast de beperkte beschikbaarheid is het de vraag of huidige methoden om HRQoL te meten daadwerkelijk meten wat het meest relevant is voor patiënten. Daarom wordt er continu gezocht naar bronnen die aanvullende informatie bieden over HRQoL. Sociale media zijn een handige en veel gebruikte communicatiebron en kunnen een potentiële optie zijn voor additionele informatie over PRO's, zoals HRQoL. Daarom hebben we in **Deel B** onderzocht hoe informatie afkomstig van sociale media HTA rapporten en beoordelingen kan ondersteunen.

Het doel van **Hoofdstuk 4** was om te beoordelen in hoeverre gezondheidsgegevens die worden gegenereerd uit sociale media inzichten kunnen bieden voor HTA. We hebben een verkennende literatuurstudie uitgevoerd om voorbeelden te identificeren in de oncologie waar gezondheidsgegevens werden verzameld via sociale media. Wetenschappelijke en grijze literatuur die gepubliceerd was tussen januari 2010 en juni 2016 werd geïdentificeerd door vier reviewers. Onafhankelijk van elkaar beoordeelden zij de studies op geschiktheid en extraheerden zij de gegevens. Op basis hiervan werd een beschrijvende kwalitatieve analyse uitgevoerd. Van de 1032 geïdentificeerde artikelen werden acht geïncludeerd: vier artikelen identificeerden bijwerkingen van kankerbehandeling, drie artikelen verspreidden HRQoL vragenlijsten, en één studie beoordeelde het voorkomen van ziektespecifieke symptomen. Verschillende sterke punten van gezondheidsgegevens gegenereerd uit sociale media werden benadrukt in de geïncludeerde literatuur, zoals de efficiënte

van het verzamelen van patiëntenervaringen en werven van patiënten met zeldzame ziekten. Daarentegen werden ook enkele beperkingen benoemd in de geïncludeerde literatuur, waaronder de validatie van authenticiteit en aanwezigheid van informatie- en selectiebias. Onze studie toonde aan dat sociale media een potentiële informatiebron kunnen vormen voor HTA, met name wat betreft aspecten zoals bijwerkingen, identificatie van symptomen, HRQoL en therapietrouw.

In **Hoofdstuk 5** lag de focus op de haalbaarheid van het gebruik van sociale media om de perspectieven van melanoompatiënten over HRQoL te verzamelen, en of huidige kanker- en melanoomspecifieke HRQoL vragenlijsten daadwerkelijk de perspectieven van melanoompatiënten vertegenwoordigen. Via de sociale mediakanalen van *Melanoma Patient Network Europe* werd een enquête verspreid. Twee onderzoekers voerden onafhankelijk van elkaar een analyse uit op de tekst om belangrijke thema's te identificeren. Deze thema's werden vervolgens vergeleken met vragen uit één huidige kankerspecifieke en twee melanoomspecifieke HRQoL vragenlijsten, namelijk de EORTC QLQ-C30, EORTC QLQ-MEL38 en FACT-M. Onze analyse toonde aan dat patiënten goede familierelaties, een normaal leven kunnen leiden en van het leven kunnen genieten de drie belangrijkste aspecten van HRQoL vonden. Verzorgers van deze patiënten gaven aan dat vanuit hun perspectief het vermogen om dagelijkse taken uit te voeren, het hebben van beheersbare bijwerkingen en pijnvrij zijn de drie belangrijkste aspecten van HRQoL voor patiënten waren. Zowel patiënten als verzorgers lijken sommige vragen uit HRQoL vragenlijsten relevant te vinden (bijv. 'Was u beperkt bij het doen van uw werk of andere dagelijkse bezigheden?') en andere minder relevant (bijv. 'Heeft u zwelling gehad in de buurt van uw melanoom?'). Bovendien lijkt de bewoording te verschillen, waarbij patiënten en verzorgers over het algemeen een positievere toon op prijs zouden stellen dan wordt gebruikt in de vragen in HRQoL vragenlijsten. Onze studie suggereert dat huidige kanker- en melanoomspecifieke HRQoL vragenlijsten, niet volledig lijken te weerspiegelen wat patiënten als belangrijk beschouwen in HRQoL. Dit roept de vraag op of informatie die wordt gegenereerd uit huidige kanker- en melanoomspecifieke HRQoL vragenlijsten gebruikt moet worden voor HTA beoordelingen of dat er alternatieve instrumenten ontwikkeld moeten worden die beter de perspectieven van patiënten met betrekking tot HRQoL weerspiegelen.

In **Hoofdstuk 6** hebben we op basis van discussies op openbare sociale mediaplatformen onderwerpen met betrekking tot HRQoL geïdentificeerd die belangrijk zijn voor melanoompatiënten. Hiervoor zijn berichten van 3 openbare online oncologieforums uit de Verenigde Staten en het Verenigd Koninkrijk

willekeurig geselecteerd. Berichten werden gecodeerd met behulp van kwalitatieve methoden totdat verzadiging was bereikt. In dit onderzoek toonden we aan dat onderwerpen gerelateerd aan angst, bezorgdheid en spanning, onzekerheid en ongunstige effecten het vaakst werden besproken tussen patiënten. We concludeerden dat online forums een waardevolle bron zijn voor het identificeren van HRQoL onderwerpen die melanoompatiënten belangrijk vinden. Deze onderwerpen zouden vergeleken kunnen worden met bestaande meetinstrumenten (zoals HRQoL vragenlijsten) om mogelijk de inhoudsvaliditeit hiervan te verbeteren. Daarnaast kunnen online forums HTA instanties ondersteunen bij de prioritering van onderwerpen en gedurende de *scoping* fase die voor een beoordeling van een nieuwe gezondheidstechnologie wordt uitgevoerd.

In **deel B** toonden we aan dat sociale media een direct beschikbare bron van informatie zijn die snel informatie kan bieden over HRQoL van patiënten met zowel zeldzame als veelvoorkomende ziekten. Het kan worden gebruikt om te luisteren naar wat patiënten online bespreken, maar ook om vragenlijsten te verspreiden. Bovendien kan informatie verkregen uit sociale media een *evidence ecosystem* ondersteunen. Hierin wordt bestaand bewijs gebruikt door verschillende stakeholders voor verschillende doelen. Deze informatiebron kan bijdragen aan een meer holistisch begrip van het perspectief van de patiënt en kwesties belichten die van invloed zijn op de HRQoL van patiënten. Gezondheidsgegevens van sociale media zijn echter vatbaar voor selectie- en informatiebias, en het valideren van de authenticiteit kan moeilijk zijn. Het is dan ook van belang om dit soort gegevens complementair te gebruiken aan traditionele vormen van onderzoek.

Potentieel van indirecte vergelijkingen voor vergoedingsbeoordelingen

Deel C bespreekt de potentie van indirecte vergelijkingen (ITC's) voor vergoedingsbeoordelingen die uitgevoerd worden door HTA instanties.

Het doel van **Hoofdstuk 7** was om de acceptatie van ITC's door HTA instanties in Nederland en Engeland te evalueren, alsook te onderzoeken of er een relatie was tussen de uitkomst van de relatieve effectiviteitsbeoordeling, kosteneffectiviteitsbeoordeling en aanbeveling voor vergoeding, en het gebruik en de uitkomst van ITC's. In eerste instantie werden alle HTA rapporten omtrent geneesmiddelen die gepubliceerd waren tussen 2015 en 2019 door het Nederlandse ZIN en het Engelse NICE opgenomen. Vervolgens werden alle volledige rapporten van ZIN meegenomen voor verdere analyse. Voor NICE

werden 100 rapporten (op basis van een willekeurige steekproef; 20 per jaar) meegenomen voor verdere analyse. Analyse van ZIN en NICE rapporten toonde aan dat ITC's regelmatig voorkwamen. Indirect bewijs kan een aanzienlijke invloed hebben op de conclusie van de relatieve effectiviteitsbeoordeling, echter het effect op de kosteneffectiviteitsbeoordeling en uiteindelijke aanbeveling is moeilijk te extraheren aangezien meerdere factoren een rol spelen. Beoordelingen van geneesmiddelen die indirect bewijs includeerden leken in drie kwart van de aanbevelingen een positieve of beperkte aanbeveling te krijgen, dit suggereert dat de evaluatie van indirect bewijs geen uitgesproken negatieve impact heeft op de toegang tot nieuwe geneesmiddelen in Nederland en Engeland. De gebruikte ITC methoden verschilden tussen de twee instanties, wat afhankelijk kan zijn van het type geneesmiddel dat wordt beoordeeld, maar ook van het beoordelingsproces van de HTA instantie. Onze resultaten ondersteunen een verdere afstemming van het proces en de methoden die voor ITC's worden gebruikt door nationale HTA instanties. Dit is met name van belang om consistente evaluaties en beoordelingen van nieuwe geneesmiddelen te waarborgen, vooral gezien de invoer van de Europese HTA regelgeving in de toekomst.

Algemene discussie

In **Hoofdstuk 8** worden de belangrijkste bevindingen samengevat en in een breder perspectief geplaatst. Hierbij worden aanbevelingen voor toekomstig onderzoek en voor praktijk & beleid gegeven.

Aanbevelingen voor toekomstig onderzoek:

- Focus op de gemeenschappelijke gronden tussen de verschillende stakeholders en de aspecten die nodig zijn om een *evidence ecosystem* te implementeren. Daarbij moet rekening worden gehouden met de taken die elk van de stakeholders heeft om ervoor te zorgen dat zij kunnen voldoen aan hun beoogde doel.
- Verder implementeren van routinematig verzamelen van PROMs in de klinische praktijk kan een focus zijn voor toekomstig onderzoek.
- Focus op de wijze waarop ITCs geïmplementeerd en geëvalueerd worden in gezamenlijke klinische beoordelingen wanneer de Europese HTA verordening van kracht wordt in 2025.

Aanbevelingen voor praktijk & beleid:

- De afstemming in definities en gebruik van gezondheidsuitkomsten vergroten tussen regulerende instanties, HTA instanties en clinici. Daarbij kan ook het begrip omtrent de verschillende taken die ieder van de stakeholders heeft worden vergroot.
- Moedig een cultuur aan waarbij gegevens en informatie wordt uitgewisseld tussen stakeholders om ervoor te zorgen dat verzamelde informatie uit de klinische praktijk, bijvoorbeeld in registers, voor meerdere processen gebruikt kan worden in het *evidence ecosystem*.
- Nationale HTA instanties moeten blijven samenwerken om ervoor te zorgen dat wanneer een *evidence ecosystem* wordt ontwikkeld en geïmplementeerd het van toegevoegde waarde zal zijn op zowel nationaal als internationaal niveau.
- Verhoog de integratie van het patiënten perspectief tijdens het HTA proces door dit te gebruiken tijdens de *scoping* fase van een HTA of om onderwerpen te prioriteren. Dit kan bijvoorbeeld door patiëntenorganisaties te betrekken of door gebruik te maken van informatie uit sociale media.
- Definieer acceptabele methoden voor ITC's die gebruikt kunnen worden voor regulerende besluitvorming, HTA beoordelingen en klinische praktijk om de ontwikkeling van een *evidence ecosystem* mogelijk te maken. Deze methoden zouden opgenomen moeten worden als onderdeel van de nieuwe methodologische richtlijnen die ontwikkeld worden als onderdeel van de gezamenlijke klinische beoordelingen onder de EU HTA verordening.
- Vergroot het systematisch verzamelen van gestandaardiseerde PROMs op basis van veilige en interoperabele systemen om ervoor te zorgen dat deze informatie beschikbaar is voor alle actoren binnen het gezondheidszorgveld.

Concluderend suggereren de studies in dit proefschrift dat de gezondheidsuitkomsten die worden gebruikt voor vergoedingsbeoordelingen grotendeels relevant zijn voor patiënten. Patiëntenperspectieven zouden echter vaker kunnen worden meegenomen gedurende de *scoping* fase of bij het prioriteren van onderwerpen. Sociale media zouden hiervoor additionele informatie kunnen bieden. Dit proefschrift toonde ook aan dat er al enige afstemming is in de gebruikte gezondheidsuitkomsten tussen de verschillende actoren in het gezondheidszorgveld. Additionele afstemming is mogelijk, maar zal niet altijd de voorkeur hebben vanwege de verschillende taken van elk van de stakeholders. Indien dezelfde gezondheidsuitkomsten worden gebruikt, kunnen indirecte vergelijkingen gebruikt worden die gebaseerd zijn op gemeenschappelijke

methodologie. Dit is echter alleen mogelijk wanneer gezondheidsuitkomsten gestandaardiseerd zijn. Dit benadrukt het belang van een gemeenschappelijke taal binnen de gehele *evidence ecosystem*.

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List of publications

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Kalf RRJ, Zuidgeest M, Delnoij DMJ, Bouvy ML, Goettsch WG. Bridging health technology assessment and healthcare quality improvement using international consortium of health outcomes measurement standard sets. *Int J Technol Assess Health Care* 2021; 38(1):e6.

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Curriculum Vitae

Rachel Kalf was born on the 8th of February 1983 in Nieuw Nickerie, Suriname. In 1986 she moved with her parents to the Netherlands.

In 2006 she obtained her bachelor's degree in Nutrition and Dietetics at the Hogeschool van Amsterdam. In the same year she started studying Nutrition and Health at Wageningen University & Research. In 2008 she obtained her master's degree as an epidemiologist. Afterwards she worked for a year at the Netherlands Institute for Health Sciences Research (NIVEL) as a junior researcher. Mid 2010 she started working as a research associate at the Erasmus Medical Center. During her time there she obtained her master's degree in Health Sciences in 2012.

In 2015 she started working as an advisor at the Dutch National Health Care Institute (Zorginstituut Nederland). First she was involved in the IMI-GetReal Project (2015-2018) and later in the IMI-GetReal Initiative (2018-2020). During her work at the Dutch National Health Care Institute she started with her PhD at the division of Pharmacoepidemiology and Clinical Pharmacology at Utrecht University in 2017. She was supervised by prof. Wim Goettsch, prof. Diana Delnoij, prof. Marcel Bouvy and dr. Anke Hövels. In 2021 she started working full-time at the Dutch National Health Care Institute again as an advisor for the Outcome-Based Healthcare Program (Uitkomstgerichte Zorg).

Currently, she is working as an epidemiologist at the Netherlands Pharmacovigilance Centre Lareb doing research regarding adverse events following immunization in children between 0 and 10 years old who receive vaccinations according to the Dutch national immunization program.