A structured review of health utility measures and elicitation in advanced/metastatic breast cancer

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Background: Health utilities are increasingly incorporated in health economic evaluations. Different elicitation methods, direct and indirect, have been established in the past. This study examined the evidence on health utility elicitation previously reported in advanced/metastatic breast cancer and aimed to link these results to requirements of reimbursement bodies.

Methods: Searches were conducted using a detailed search strategy across several electronic databases (MEDLINE, EMBASE, Cochrane Library, and EconLit databases), online sources (Cost-effectiveness Analysis Registry and the Health Economics Research Center), and websites of health technology assessment (HTA) bodies. Publications were selected based on the search strategy and the overall study objectives.

Results: A total of 768 publications were identified in the searches, and 26 publications, comprising 18 journal articles and eight submissions to HTA bodies, were included in the evidence review. Most journal articles derived utilities from the European Quality of Life Five-Dimensions questionnaire (EQ-5D). Other utility measures, such as the direct methods standard gamble (SG), time trade-off (TTO), and visual analog scale (VAS), were less frequently used. Several studies described mapping algorithms to generate utilities from disease-specific health-related quality of life (HRQOL) instruments such as European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Breast Cancer 23 (EORTC QLQ-BR23), Functional Assessment of Cancer Therapy – General questionnaire (FACT-G), and Utility-Based Questionnaire-Cancer (UBQ-C); most used EQ-5D as the reference. Sociodemographic factors that affect health utilities, such as age, sex, income, and education, as well as disease progression, choice of utility elicitation method, and country settings, were identified within the journal articles. Most submissions to HTA bodies obtained utility values from the literature rather than exploring the HRQOL data obtained during clinical development. This was critiqued by the National Institute for Health and Clinical Excellence (NICE). Furthermore, the impact of age on utilities was highlighted by NICE and it was suggested that an age match of the study population should be attempted.

Conclusion: Health utilities are recorded across the globe to varying extents and using differing elicitation methods. Manufacturers seeking reimbursement need to be aware of the country-specific requirements for elicitation of health utilities.

Keywords: health utilities, advanced/metastatic breast cancer, health-related quality of life, health technology assessment, HTA, direct utility measures, indirect utility measures

Background
Breast cancer is the most commonly diagnosed cancer among women worldwide, one in eight women being diagnosed in their lifetime in the US1; in Europe, 464,000 new
cases are estimated to have been diagnosed in 2012, 13.5% of all cancer cases. Approximately 5%–10% of breast cancers diagnosed are metastatic/advanced in nature, and of these, approximately one-fifth survive for a period extending up to 5 years. Although significant advances in treatment have been made in recent years, metastatic/advanced breast cancer continues to provide challenges for the health care system. In addition, disease recurrence at a distant metastatic site is common, occurring in as many as 30% of women initially diagnosed with an earlier-stage breast cancer. The focus of this manuscript is on metastatic/advanced breast cancer.

Patients with breast cancer often undergo several rounds of treatment during which they endure adverse events and toxicity. This affects the health-related quality of life (HRQOL), which can be measured during trials using generic or disease-specific HRQOL instruments, such as the European Quality of Life Five-Dimensions questionnaire (EQ-5D) or the Functional Assessment of Cancer Therapy – General questionnaire (FACT-G), respectively. Breast cancer is associated with a decrease in HRQOL, particularly in patients with advanced/metastatic breast cancer.

Reimbursement decision makers are interested in the efficacy of treatments, and economic analyses are increasingly being utilized when comparing care settings and treatment modalities. A cornerstone of such analysis is the quality-adjusted life year (QALY), which incorporates both the quantity and the quality of life (QOL) lived generated by health care interventions. QALYs are therefore the arithmetic product of life expectancy and a measure of the quality of the remaining life-years. QALYs are used in cost–utility analysis (CUA), in which cost of treatment is related to survival and QOL, and they are also used to support health technology assessment (HTA) submission and reimbursement decisions.

To facilitate calculation of QALYs, the QOL part has to be a health preference or health utility measure rated on a scale from 0 (dead) to 1 (full health). Several approaches have been developed to elicit health utilities. Direct measures such as time trade-off (TTO) and standard gamble (SG) can be used for discrete condition-specific health states. The visual analog scale (VAS) method is another commonly used direct measure.

On the other hand, indirect measures utilize validated HRQOL instruments, either generic (eg, EQ-5D) or disease-specific (eg, FACT-G), for well-defined health states. As HRQOL instruments do not directly return utility values, an algorithm is necessary to assign values to the responses from a social tariff or value set, which can be derived from patients or the general population using TTO or SG. The choice of health utility measure often depends on several factors; the study question, mode of action of a therapy, the impact on the patient, the availability of country-specific guidelines detailing what is acceptable, and whether the aim is to support clinical or policy decisions, are factors that can potentially influence the choice of measure.

The preferred utility elicitation method, as also outlined by the European Network for Health Technology Assessment (EUnetHTA) guidelines, in several European countries is indirect elicitation using the generic EQ-5D. This tool enables comparability of interventions across different technologies and disease areas. It is further recommended that the used value set be based on preferences representing the general population. However, TTO is considered appropriate/acceptable by some HTA bodies when EQ-5D is not appropriate. Valuation of the health states by the general public is recommended, as resource allocation in a publically funded health care system should be weighted by the general public’s perception of disease burden. Because perception of disease burden can vary among the population due to experience as well as sociodemographic factors (eg, age, sex, education, and income), utilities could be affected by these factors.

The objective of this study was two-fold: to identify health utility measures previously used in advanced/metastatic breast cancer, and to understand how these factors may influence future economic evaluations of metastatic/advanced cancer therapies. This article reports on the results obtained from a broad review of the published literature and health economic databases and thereafter aims to link these results to the requirements of reimbursement bodies to support decision making.

**Methods**

A targeted literature search was conducted electronically to identify international publications relating to health utilities in advanced/metastatic breast cancer. The following databases were used in OVID (OVID Technologies, Inc); MEDLINE and MEDLINE (R) In-Process (PubMed), EMBASE (OVID), EconLit (EBSCOhost), and the National Health Service (NHS) Economic Evaluation Database (NHS-EED). The search used a combination of disease-specific terms (breast cancer, metastatic, and advanced) and health utility-specific terms (standard gamble, time trade-off, EQ-5D, Health Utilities Index [HUI1, HUI2, HUI3], Short Form – Six-Dimension [SF-6D]) and their derivatives (such as SG for standard gamble). In addition, a search string was used to identify cost-effectiveness, cost utility, cost benefit, cost minimization, cost evaluation, or cost analysis studies [cost* adj2 (effective* Or utilit* Or ben-
efit* Or minimi* Or evaluat* Or analy*)]. “*” and “adj” are search commands utilized in the database search to increase both sensitivity and specificity of the searches. The search was limited to studies on humans published in English language only, between January 2005 and March 2015, to identify the most up-to-date literature. Studies for full-publication review were selected for inclusion on the basis of the search strategy and the overall objectives of the study. When determining the most relevant articles for full review, prioritization was given to publications placing greater emphasis on utility measure utilization as the primary objective.

In addition to the targeted literature review, a gray literature search was undertaken to identify supplementary evidence that would augment findings in areas not well reported in the published literature. Databases within which the gray literature search was conducted included the Cost-effectiveness Analysis (CEA) Registry, the Health Economics Research Center (HERC) database of mapping studies, and the database of the International Network of Agencies for Health Technology Assessment (INAHTA). A review of breast cancer product submission documents from HTA bodies in the UK (the National Institute for Health and Clinical Excellence [NICE], Scottish Medicines Consortium [SMC], and All Wales Medicines Strategy Group [AWMSG]) was also conducted to inform understanding of manufacturers’ different approaches in generating utility data in advanced/metastatic breast cancer and their acceptability by HTA bodies. In addition, EUenetHTA guidance documentation was reviewed to gain further insight from the wider European HTA perspective.\(^\text{12}\)

An overview of the study methodology is presented in Figure 1.

### Results

#### Summary of the literature review results

A total of 768 potentially relevant publications were identified in the searches; 748 were identified in the OVID search, 20 in the gray literature search, including ten HTA submissions. When assessed for inclusion, 26 studies/publications – 18 journal articles and eight HTA submissions – were deemed relevant as they contained material related to utility measures in advanced/metastatic breast cancer. Journal articles of studies that derived utility measures/values from the literature were excluded at the screening stage.

The journal articles reviewed in this review comprise studies that fall in three categories. The first category included studies (n=11) that use HRQOL measures, both generic (eg, EQ-5D) and disease specific, to describe patient health status/QOL and elicit health utilities with the potential use of these utilities in future economic evaluations.\(^\text{9,14–23}\) The second group comprised studies (n=3) that described the development and/or validation of mapping algorithms between disease-specific HRQOL measures and generic utility measures to predict breast cancer utility values from disease-specific HRQOL outcomes measures for use in future economic evaluations.\(^\text{24–26}\) The third category contained health economic evaluations (n=4), including cost–utility studies, which elicit health utilities during the study to be incorporated in a health economic model.\(^\text{27–30}\) A summary of the key findings from the literature review, detailing the main trends observed, is presented here.

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**Figure 1** Overview of methodology.

**Abbreviations:** AWMSG, All Wales Medicines Strategy Group; HTA, health technology assessment; INAHTA, International Network of Agencies for Health Technology Assessment; NICE, National Institute for Health and Clinical Excellence; SMC, Scottish Medicines Consortium.
**Table 1 Utility and health-related quality of life measures reported in the identified journal articles**

<table>
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<th>Direct measures</th>
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<th>Utilities collected?</th>
<th>Mapping/ conversion</th>
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Notes:
- a EORTC QLQ-C30 outcomes were mapped onto EQ-5D using a mapping algorithm previously developed for gastric cancer.
- b Cheng et al utilized a multiattribute utility scoring formula, based on SG utilities derived from the power conversion of VS (VAS) scores.

Abbreviations:
- EQ-5D, European Quality of Life Five-Dimensions questionnaire
- 15D, 15-Dimensions questionnaire
- SF-6D, Short Form – Six-Dimension
- TTO, time trade-off
- SG, standard gamble
- VAS, visual analog scale
- VS, visual scale
- FACT-G, Functional Assessment of Cancer Therapy – General questionnaire
- Fact-B, Functional Assessment of Cancer Therapy – Breast
- EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
- EORTC QLQ-BR23, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Breast Cancer
- UBQ-C, Utility-Based Questionnaire-Cancer
- HRQOL, health-related quality of life
- HER2, human epidermal growth factor receptor 2.
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Notes: EORTC QLQ-C30 outcomes were mapped onto EQ-5D using a mapping algorithm previously developed for gastric cancer. Cheng et al utilized a multifactor utility scoring formula, based on 5G utilities derived from the power conversion of VS (VAS) scores.

Abbreviations: EQ-5D, European Quality of Life Five-Dimensions questionnaire; 15D, 15-Dimensions questionnaire; SF-6D, Short Form – Six-Dimension; TTO, time trade-off; SG, standard gamble; VAS, visual analog scale; VS, visual scale; FACT-G, Functional Assessment of Cancer Therapy – General questionnaire; FACT-B, Functional Assessment of Cancer Therapy – Breast; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EORTC QLQ-BR23, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Breast Cancer 23; UBQ-C, Utility-Based Questionnaire-Cancer; HRQOL, health-related quality of life; HER2, human epidermal growth factor receptor 2.
Eight of the identified journal articles utilized diseasespecific HRQOL instruments, including the cancer-specific FACT-G, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30), and Utility-Based Questionnaire-Cancer (UBQ-C), as well as breast cancer-specific FACT-B and EORTC QLQ – Breast Cancer 23 (EORTC QLQ-BR23) (Table 1). EORTC QLQ-C30 was the most commonly used instrument, used in five studies. Six of the eight studies used disease-specific instruments (EORTC QLQ-C30 and -BR23; FACT-G and -B) alongside EQ-5D or TTO-and-SG, and three studies subsequently mapped the responses to EQ-5D.24–26 Only one study, from Australia, reported use of the cancerspecific measure UBQ-C and the subscales were converted to a utility index.15

The direct elicitation tools SG and TTO have been identified in six17,18,20,22,27,29 and five9,14,19,20,28 journal articles, respectively. SG and TTO have mainly been used as the sole utility measures. One study used both measures, however, for different purposes; SG was used to derive utilities for five breast cancer disease states, while TTO was used to derive utilities for three new therapeutic modalities.20 This cited study viewed TTO as being less complex than SG for assessing temporary health state utilities related to 1-year descriptions for treatment and recovery.20 Additionally, TTO was used in two studies alongside EQ-5D19 to obtain utility values. This enabled Lidgren et al9 to describe the differences in utilities when using HRQOLs based on community preferences (EQ-5D social tariffs) versus those based on patient preferences (TTO). In this study, mean TTO utility values were higher for all four breast cancer disease states compared to the EQ-5D index values, three of which were statistically significant (P<0.05).9 Similarly, Milne et al19 generated utilities in breast cancer using both a direct and an indirect method, allowing for analysis of the differences in utility values. The mean and the median utility valuations obtained by using the TTO method were generally higher for three of the four health states than those from other methods (EQ-5D and VAS).19

The VAS technique, otherwise known as the rating scale, is often used as a HRQOL measure and can be used to elicit utility values via conversion formulas. A total of nine publications reported on the use of VAS.9,14,16,18,19,22,23,25,29 In all of these, VAS was used in addition to other measures, mainly EQ-5D (often as EQ-5D VAS), but also TTO and SG. In only three publications was VAS used to derive the utility values by itself.19,22,29

Mapping of disease-specific HRQOL measures to utility instruments

Disease-specific HRQOL measures are commonly used to evaluate HRQOL in patients with cancer. Utilities can also be obtained indirectly from disease-specific HRQOL measures, which can be more sensitive than generic ones. These measures do not have utility scoring systems and translating the HRQOL outcomes of these instruments into utility values requires mapping to preference-based measures, such as the EQ-5D questionnaire.22

In three identified journal articles, mapping studies have been described with the aim of developing algorithms that can be used in future research.24–26 In these publications, different instruments have been administered in parallel and the results have been used to develop mapping algorithms. Crott and Briggs26 developed algorithms to map the cancer-specific EORTC QLQ-C30 to EQ-5D, while Kim et al25 mapped the cancer-specific EORTC QLQ-C30 as well as its breast cancer-specific module EORTC QLQ-BR23 to EQ-5D. The latter showed that EORTC QLQ-C30 was better suited to mapping to EQ-5D than EORTC QLQ-BR23 as errors in the first case were observed to be smaller. Teckle et al24 mapped the cancer-specific questionnaire FACT-G to both EQ-5D and SF-6D, showing that mapping of FACT-G to either EQ-5D or SF-6D was feasible. An additional study used a mapping algorithm previously developed for gastric cancer to map EORTC QLQ-C30 to 15-Dimensions (15D) and EQ-5D in patients with breast cancer to evaluate the cost utility of adjuvant therapies.30

Factors that might influence health utility values

Factors such as sociodemographic characteristics of the study population (eg, age and sex), disease progression, country setting, and choice of instrument influenced the magnitude of health utility values.

Sociodemographic factors

In order to assess the effect of intrapopulation differences on the elicited utilities, baseline sociodemographic factors, including age, sex, ethnicity, household income, education, and marital status, were analyzed in two studies.18,20

The impact of age was investigated in both studies.18,20 Lloyd et al18 found that people aged 50 years rated stable metastatic disease on treatment with no side effects, a higher utility value than people aged 40 years (0.77 versus 0.72). In contrast, mean utility values for five breast cancer dis-
ease states in the study by Schleinitz et al.\textsuperscript{20} were lower for patients aged $\geq 50$ years compared to those aged $\leq 50$ years, albeit not statistically significant (eg, disease stage III: 0.51 versus 0.61). It should be noted that the health states are not comparable between these two publications. The impact of sex was identified in one study, with male participants showing greater decline in utility associated with disease progression compared to female participants.\textsuperscript{18} The authors suggested that female participants considered family responsibilities and child care more in rating health states and so were less willing to accept risks to avoid progression of disease.\textsuperscript{18} Ethnicity, household income, and education were also shown to influence utilities.\textsuperscript{20} For example, results from the study by Schleinitz et al.\textsuperscript{20} showed that being black, having a household income of $<25,000$, or having less education resulted in lower utilities in less severe disease states (stages I–III).\textsuperscript{20} This was statistically significant in one-way analysis of variance analysis ($P$-values for each disease stage ranged from $<0.001$ to 0.01).\textsuperscript{20} Mean utilities for hormonal treatment were demonstrated to be higher in white people than other ethnicities, while they were lower for those from a lower-income household.\textsuperscript{20} Additionally, being single also resulted in lower mean utilities for all treatment options (chemotherapy, hormonal therapy, and radiation therapy).\textsuperscript{20}

**Disease progression**

Lidgren et al.\textsuperscript{9} showed that disease progression affected utility values, with patients showing utilities of 0.901, 0.842, 0.889, and 0.820 for the first year after primary cancer, first year after recurrence, second and following years after primary cancer/recurrence, and metastatic disease, respectively. Schleinitz et al.\textsuperscript{20} demonstrated a similar pattern in which the overall mean utilities of less severe disease stages were higher compared to mean utilities in more severe disease stages (decrease from 0.68 in stage I of tumor, node, metastasis classification of the American Joint Committee on Cancer versus 0.41 in stage IV).

**Instrument type**

Comparing the performance of different elicitation methods showed that utility values varied between the methods. For example, mean TTO values were consistently higher than the mean EQ-5D values for all four defined disease states studied by Lidgren et al.\textsuperscript{9} The difference between the two sets of values was statistically significant for three of the four states.\textsuperscript{9}

**Country requirements**

Differences among countries may result in differences in utility values. For example, in a study by Frederix et al.\textsuperscript{14} the TTO-derived utilities for nine breast cancer health states were collected from two different cohorts, one in the Netherlands and one in Sweden. Of these, the Swedish sample rated progressive and stable disease health states (0.61 and 0.81, respectively) higher than the Dutch sample (0.49 and 0.69, respectively).\textsuperscript{14} Frederix et al.\textsuperscript{14} demonstrate that this is due to the fact that both countries have different reimbursement criteria when it pertains to utility collection. The Netherlands advocates preferences to be representative of the general public. In contrast, the Swedish reimbursement agencies prefer obtaining utilities from the same demography as people with the disease of interest, resulting in this cohort containing a larger number of older females.\textsuperscript{14}

As the Swedish study population was generally older, they may have had a different perspective when they were asked to consider trading years of life in the TTO task compared to the younger Dutch sample. Furthermore, although utilities were not generated from EQ-5D outcomes, the Swedish cohort reported worse health status based on EQ-5D than the Dutch population. It is suggested by Frederix et al.\textsuperscript{14} that older people are likely to be less concerned about the prospect of poor health states as they have already experienced poor health, resulting in higher preference weights for poor health states.\textsuperscript{14}

**HTA submission documents**

A total of eight HTA documents submitted to NICE, AWMSG, or SMC contained information related to advanced/metastatic breast cancer utilities, along with comments from the HTA bodies. In all submissions, the manufacturer used SG-derived utilities obtained from the literature, most often from the study by Lloyd et al.,\textsuperscript{18} in which utilities were collected from members of the UK general public ($n=100$). In five submissions, the manufacturer recorded HRQOL data (EQ-5D,\textsuperscript{31} FACT-B,\textsuperscript{32–34} and EORTC QLQ-C30)\textsuperscript{35} during the clinical studies; however, only in two were utility values generated from these data.\textsuperscript{31,34} In one submission to the AWMSG, the manufacturer utilized EQ-5D administered during a trial to generate utility values,\textsuperscript{31} while one of the NICE submissions used a mapping algorithm to obtain utility values using FACT-B data obtained in their trial.\textsuperscript{34} One submission did not detail the method utilized to generate utilities.\textsuperscript{36}

The main concerns of the appraisal committee and the evidence review group were 1) use of SG utility values from
the study by Lloyd et al, as the age of the population in that study did not match the age of patients with breast cancer or of the trial population, and 2) the absence of mapping of disease-specific HRQOL data to utility indexes. Additionally, the NICE committee was concerned about omission of adverse event disutilities from base-case models. Of these, the choice of method matters as the differences in theory and approach can lead to differences in utility valuation. For example, a review of utilities by Morimoto and Fukui across 907 chronic and 86 acute health states reported a clear trend of VAS yielding the lowest and SG yielding the highest utility values for the same health states, with TTO lying in between. 

The evidence showed that the disease-specific HRQOL instruments, FACT-G, FACT-B, EORTC QLQ-C30, and EORTC QLQ-BR32, were only used alongside EQ-5D. In most cases, these instruments conveyed HRQOL data rather than eliciting health utilities.

One approach to transform responses of disease-specific HRQOL instruments to utilities is mapping to generic measures. Authors of a few identified publications have explored this approach successfully, generally mapping disease-specific HRQOL instruments to EQ-5D. Mapping approaches are accepted by HTA bodies in several European countries (eg, England, Scotland, Italy, and Norway) in cases where there are no other data available. In cases where mapping is used, the preferred approach by NICE and SMC is to map to EQ-5D. However, other European countries (eg, France) advise against mapping due to the uncertainties of mapping functions. Among the identified HTA submissions to AWMSG, NICE, or SMC, only one used a mapping approach. Two other HTA submissions were critiqued by NICE for not attempting mapping despite manufacturers reporting HRQOL data using EORTC QLQ-C30 or FACT-B during clinical development. In one case, it was highlighted that no HRQOL data were obtained during the trial. NICE conducted a pilot study for the feasibility of obtaining robust EQ-5D data for patients with breast cancer in UK clinical practice. Even though the study showed that it was feasible to collect data in such a setting, the logistics were complex and the authors recognized the merits of obtaining utility data from published estimates and trial data.

In the identified publications, several factors that affect utilities were reported, including sociodemographic characteristics of the study population (eg, age, income, and education), disease or health states, elicitation method, and country settings, which ultimately influence the decision making.
process. During health economic evaluation, utility values are frequently taken from published literature. HTA bodies such as NICE and SMC emphasized that such an approach should be undertaken with diligent care; if possible, published utilities should be age-matched to the relevant tariff score, and the health states used when generating utility values should match that of the trial population. In addition, most HTA bodies have their country-specific requirements for elicitation methods (direct or indirect), value sets when using indirect elicitation methods, and use of mapping algorithms.

The literature review was restricted to advanced/metastatic breast cancer and publications in English language of the past 10 years (January 2005–March 2015). This approach might have limited the number of publications identified. In addition, publications that used utility values reported in the literature were excluded as these did not add to the evidence base. The second aim of this literature review was to understand how these factors may influence future economic evaluations of metastatic/advanced cancer therapies. However, only a few manufacturer submissions were identified during the study time frame, limiting data availability from the reimbursement perspective and generalizability. Furthermore, out of the identified eight submissions to AWMSG, NICE, or SMC, seven therapies were not recommended; therefore, critique on the utility part within the submission was limited. Payer and decision maker perspectives outside of HTA bodies were not a focus of this review but undoubtedly could add another dimension when considering choice of utility elicitation.

Conclusion

Based on the results of this literature review, health utility elicitation methods varied widely across the targeted review for advanced/metastatic breast cancer. EQ-5D was the most commonly used measure, with the direct utility measures SG and TTO also highly represented in the review; this is in line with many European guidelines on health economic evaluations and recommendations from HTA bodies. Although a number of cancer-specific instruments were utilized, there is a lack of publications and HTA submissions reporting advanced/metastatic breast cancer health state utilities derived from breast cancer-specific instruments. In addition to choice of elicitation method, other factors – such as sociodemographic characteristics of the study population, disease or health states, and country settings – need to be taken into consideration when deriving health utilities for policy decision makers. Additional qualitative research discussing advanced/metastatic breast cancer health state utilities from a payer and/or reimbursement decision maker perspective may offer additional insights.

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Author contributions

JC and VW participated in the study conception and design, analysis and interpretation of literature, write up and review of the manuscript for important intellectual content, and approved the manuscript for publication. YH participated in the study conception and design, reviewed, and approved the final version of the manuscript. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

JC and VW were employees of Adelphi Values at the time the research was conducted. YH is currently an employee of Novartis. The authors report no other conflicts of interest in this work.

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