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Vignette-Based Utilities: Usefulness, Limitations, and Methodological Recommendations

Louis S. Matza, PhD, Katie D. Stewart, MA, Andrew J. Lloyd, DPhil, Donna Rowen, PhD, John E. Brazier, PhD

ABSTRACT

Health technology assessment agencies often prefer that utilities used to calculate quality-adjusted life years in cost-utility analyses (CUAs) are derived using standardized methods, such as generic preference-based measures completed by patients in clinical trials. However, there are situations when no standardized approach is feasible or appropriate for a specific medical condition or treatment that must be represented in a CUA. When this occurs, vignette-based methods are often used to estimate utilities. A vignette (sometimes called a "scenario," "health state description," "health state vignette," or "health state") is a description of a health state that is valued in a preference elicitation task to obtain a utility estimate. This method is sometimes the only feasible way to estimate utilities representing a concept that is important for a CUA. Consequently, vignette-based studies continue to be conducted and published, with the resulting utilities used in economic models to inform decision making about healthcare resource allocation. Despite the potential impact of vignette-based utilities on medical decision making, there is no published guidance or review of this methodology. This article provides recommendations for researchers, health technology assessment reviewers, and policymakers who may be deciding whether to use vignette-based methods, designing a vignette study, using vignette-based utilities in a CUA, or evaluating a CUA that includes vignette-based utilities. Recommendations are provided on: (A) when to use vignette-based utilities, (B) methods for developing vignettes, (C) valuing vignettes, (D) use of vignette-based utilities in models, and (E) limitations of vignette methods.

Keywords: cost-utility analysis, health state utilities, health state vignettes, time trade-off, utility assessment, vignette-based methods

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Introduction

Health technology assessment (HTA) agencies often prefer that utilities used to calculate quality-adjusted life years in cost-utility analyses (CUAs) are derived from generic preference-based measures (GPBMs) completed by patients in clinical trials.[1] For example, the influential guide from the National Institute for Health and Care Excellence (NICE) in the United Kingdom indicates a preference for utilities derived via the EQ-5D to maximize "consistency across appraisals."[2] The guide adds that utilities derived via other methods may be acceptable when the EQ-5D is not "available" or "appropriate." When dimensions of available GPBMs are not appropriate for a specific medical condition or treatment, researchers can consider alternative preference-based measures, including condition-specific preference-based measures (CSPBMs) or a "bolt-on" approach in which a condition-specific item is added to a GPBM.[3–5] When no preference-based data from a trial are available, it may be possible to generate utilities by mapping from a patient-reported outcome measure to a GPBM.[6,7] However, there are situations when no standardized approach is feasible or appropriate for a specific medical condition or treatment that must be represented in a CUA. When this occurs, vignette-based methods are often used to estimate utilities.[8,9]

In these studies, a vignette is a description of the impact of a medical condition that is valued in a preference elicitation task to obtain a utility estimate. Vignettes may describe a medical condition, its treatment, and its impact on various domains of health-related quality of life (HRQL). The vignettes may be called "scenarios," "health state descriptions," "health state vignettes," or "health states." For decades, this approach has been used to derive utilities for a wide range of medical and psychiatric conditions.[10–23] Vignette-based utilities are often published and used in CUAs conducted to inform decision making about healthcare resource allocation in multiple countries. Although some HTA guidelines do not explicitly mention the role of vignette-based utilities,[2,24] others list vignette methods as one of the options for estimating utilities.[25,26] A substantial portion of CUAs submitted to NICE use utilities that deviate from the recommended EQ-5D approach, including utilities based on vignettes.[8,9]

Despite the ongoing use of vignette-based methods with potential impact on economic modeling and healthcare resource allocation, there is no published guidance or review of this

methodology. Therefore, the purpose of this article is to provide recommendations for researchers deciding whether to use vignette-based methods, designing a study, or using resulting utilities in a CUA. This article includes the following sections: (A) when to use vignette-based utilities, (B) methods for developing vignettes, (C) valuing vignettes, (D) use of vignette-based utilities in models, and (E) limitations of vignette methods.

A. When to Use Vignette-Based Utilities

Before initiating a vignette-based study, it is essential to consider whether there is justification for this method rather than generating utilities by having patients complete a preference-based instrument such as the EQ-5D,[27] Health Utilities Index (HUI),[28] or a CSPBM. One advantage of the vignette approach is that it can be used to estimate utilities for medical conditions and treatment attributes that may be difficult or impossible to obtain via preference-based measures, mapping, or published literature. Five situations in which vignette methods may be useful are described below and summarized in Table 1.

1. Patients Who Are Difficult to Access

With some groups of patients, it may not be possible to recruit a large enough sample to complete preference-based measures. A vignette-based study, with vignettes valued by general population respondents, may be the only feasible method for estimating health state utilities needed for a model. For example, vignette methods are often used to estimate utilities for rare diseases, where the sample size of any patient data would be insufficient to represent all disease states required for an economic model. Examples include beta thalassemia,[29] familial chylomicronemia syndrome,[30] hemophilia,[23] pemphigus,[31] inherited retinal disease,[15] hypophosphatasia,[32] and neuroendocrine tumors.[33]

Patients with debilitating impairment or highly intensified treatment may also be difficult to access for completion of GPBMs. Examples include patients who are receiving inpatient psychiatric treatment, unconscious, in acute phases after stroke,[34] or undergoing inpatient chemotherapy or stem cell transplant.[35] Some pediatric samples are also difficult to access for completion of GPBMs.[36,37]

2. Isolating the Utility Impact of Specific Attributes

Sometimes, CUAs require utilities representing the impact of a single symptom, adverse event (AE), or treatment attribute. Although generic instruments can be sensitive to specific symptoms, such as pain, they may not be able to isolate the utility impact of a single attribute because the scores they yield are influenced by broader aspects of the patient experience. In contrast, with the vignette approach, it is possible to isolate the utility impact of a single attribute. For example, to estimate the disutility of an AE not captured by a GPBM, utilities can be derived for 2 vignettes that are identical except for the addition of the AE

Table 1. Situations when vignette-based methods are commonly used to estimate health state utilities.

Situation	Brief description	Examples of relevant vignette-based studies
1. Patients who are difficult to access	With some groups of patients, it may not be possible to recruit a large enough representative sample to complete preference-based measures. A vignette study may be the only feasible way to estimate utilities to represent these health states in a model (eg, rare diseases, young children, patients with debilitating impairment or highly intensified treatment).	Lloyd et al[32] Lloyd et al[15] Matza et al[29] Matza et al[30] Prosser et al[36] Rencz et al[31] Saigal et al[37] Steen Carlsson et al[23] Swinburn et al[33]
2. Isolating the utility impact of specific attributes	By keeping all aspects of a vignette constant except for a single attribute, it is possible to isolate the utility impact of a single characteristic, such as a symptom, adverse event, or treatment attribute. Although GPBMs can be sensitive to some specific symptoms, such as pain, these instruments may not be able to isolate the specific utility impact of a single attribute relevant to a CUA.	Boye et al[38] Fordham et al[39] Lloyd et al[40] Matza et al[43] Matza et al[41] Matza et al[16] Shingler et al[44]
3. Treatment process utilities	Utilities can be used to quantify the impact of treatment process attributes, such as mode of administration, dose frequency, medical device attributes, and treatment convenience. A GPBM is unlikely to be sensitive to utility differences stemming from specific treatment process attributes. Consequently, process utilities are usually estimated using vignette-based methods.	Boye et al[49] Davies et al[50] Krassioukov et al[53] Lloyd et al[54] Matza et al[56] Matza et al[17] Matza et al[16] Steen Carlsson et al[23]
4. Acute and temporary health states	Some medical conditions involve flares or exacerbations. It can be difficult to administer a preference-based measure to patients at the time of these temporary events. Vignette-based methods can be used to estimate a disutility in this situation.	Matza et al[71] Matza et al[30]
5. Health states that change over time	A "path state" vignette can represent a patient proceeding through a sequence of temporary experiences in a typical course of a medical condition and its treatment.	Kuppermann et al[72] MacKeigan et al[73] Matza et al[34] Matza et al[74] Matza et al[29]

AE indicates adverse event; CUA, cost-utility analysis; GPBM, generic preference-based measure.

to one of the health states. The utility difference score between these 2 otherwise identical vignettes can be attributed entirely to the AE, and would therefore represent the disutility (ie, utility decrease) associated with the AE. This approach has been used to estimate the utility impact associated with a range of patient experiences.[16,38-44]

3. Treatment Process Utilities

A growing body of research suggests that utility may be influenced not only by health status, but also by the process of receiving care.[45-48] These "process utilities" quantify the impact of attributes such as mode of administration, dose frequency, medical device attributes, and aspects of treatment convenience that may have an impact on patients' quality of life.[16,17,23,49-57] Treatment process usually has less impact on utility than efficacy, safety, or symptom severity,[43] but it is often important to patients. Furthermore, treatment process could affect treatment adherence, which can influence outcomes.[58-60] Therefore, it may be useful to include process utilities in some CUAs.

A generic instrument designed to assess overall health status is unlikely to be sensitive to utility differences stemming from specific treatment process attributes. Consequently, process utilities are usually estimated using alternative approaches such as a preference-based index focused on a specific treatment process, discrete choice experiments, and most frequently, time trade-off (TTO) valuation of health state vignettes.[45,46,48,61] As with AEs, the vignette approach can isolate the utility impact of a specific treatment process attribute by holding all aspects of a health state constant except for this attribute. Process utilities estimated with vignettes have been included in CUAs conducted for HTA submissions,[38,41,62] and favorable HTA impressions of cost-effectiveness suggest that these process utilities can be useful model inputs.[63-66]

4. Acute and Temporary Health States

Some medical conditions involve flares or exacerbations, and a CUA assessing the value of treatment for these conditions may require utilities for these temporary events.[67-69] In some clinical trials, it may be possible to administer a GPBM frequently so that utility is likely to be assessed at the time of events that are relevant to subsequent economic modeling.[69,70] However, when events are infrequent, it can be challenging to administer a measure to estimate utilities at the time they occur. In these situations, the disutility of an acute event can be estimated by valuing vignettes with and without the acute event. The utility difference between these 2 vignettes would represent the disutility of the event. For example, this approach has been used to estimate quality-adjusted life year decrements of skeletal-related events associated with bone metastases.[71]

5. Health States That Change Over Time

Preference-based measures assess utility at the time patients complete the instrument. To estimate the utility of a health experience that changes over time, a preference-based measure would have to be administered at multiple time points corresponding to key health experiences, which can be challenging. To estimate utilities of a medical condition that changes over time, one could consider a vignette approach. Vignettes called "path states" can represent a hypothetical patient proceeding through a sequence of temporary experiences, including the typical course of a medical condition and its treatment.[29,34,72,73] Respondents who value the health states are asked to consider the full path including the duration of time spent in each part. For example, a recent vignette study was designed to estimate the disutility of a surgical site infection.[74] Because a patient's condition changes rapidly after the unexpected infection, it is usually infeasible to administer measures to patients at multiple precise time points to capture the utility impact of the full experience. With the vignette approach, it was possible to estimate a disutility of the full sequence of events including the infection, antibiotic treatment, surgical intervention, and gradual resolution of symptoms.

B. Developing Vignettes

Health state vignettes should be developed in the following steps (Fig. 1).

1. Determine the Number of Vignettes and Level of Detail in the Vignettes

First, it is necessary to decide which vignettes should be developed. Like any utility estimation study, it is important to consider the anticipated CUAs to ensure that the resulting health state utility values will be useful.[68] Model specifications will help determine the number of vignettes and the required specificity of each vignette. Sometimes, a general description may be used to represent a wide range of patients. Other times, more vignettes may be needed so that greater granularity in patient characteristics can be represented in a CUA.

The number of health states that can be valued by each respondent depends on the length and complexity of each health state. Vignette content should be as brief and simple as possible, while providing the information necessary to understand the health state. With less information, participants are more likely to attend to every detail, understand the health state content, identify the differences among health states, and avoid logical inconsistencies in utilities. With longer vignettes, respondents are more likely to skip, ignore, or forget content, possibly resulting in inconsistent, illogical, or uninformed valuations.

2. Obtain Evidence to Inform Vignette Content

Vignettes must be supported by the best available evidence so that the resulting utilities can be trusted as reliable estimates. Ideally, multiple sources of support will be used, and methods for gathering this information should be thoroughly presented in the methods sections of publications.

Vignettes should be supported by citations, including published scientific literature, information from established medical organizations (eg, American Diabetes Association), medication labels, and/or medical device instructions for use. Published qualitative studies eliciting the patient perspective may be particularly helpful for drafting vignette language.

Vignettes are often developed based on interviews with individuals who have insight into the medical condition or treatment, including patients, clinicians, and/or caregivers. Patients can explain their personal experience in simple language that may inform the health state descriptions, while highlighting the most bothersome symptoms. However, some experiences reported by individual patients may be unusual or unique, and it is necessary to determine which aspects of a patient's report are typical rather than idiosyncratic. Therefore, quotations from individual patients should be considered in combination with other sources of information.

Clinicians who see many patients may be the most common source of vignette support because they can describe the typical patient experience based on the range of patients they have treated. Physicians are often interviewed, but other types of clinicians may have more direct contact with patients, leading to

Figure 1. Suggested good practices for development of health state vignettes.

1. Determine the number of vignettes that will be developed, along with the expected level of detail. These decisions should be based on anticipated modeling needs, while considering feasibility of the eventual valuation task.
2. Obtain evidence to inform vignette content. Vignettes must be supported by the best available evidence. Possible sources of support include:
   - Publicly available citations including published scientific literature, information from established medical organizations, medication labels, and/or medical device instructions for use
   - Qualitative interviews (or group discussions) with individuals who have insight into the relevant medical condition or treatment (e.g., patients, clinicians, caregivers)
   - Quantitative data (e.g., patient-reported outcome measures in clinical trials)
   - Qualitative analysis of social media data such as online patient discussion forums
3. Draft the health state descriptions. General principles include:
   - Vignettes should be designed to maximize comprehension (e.g., brief descriptions, simple language, avoid medical jargon)
   - Vignettes should represent the typical patient experience
   - Vignettes should be designed to facilitate comparison between health states with parallel structure when appropriate
   - Supplemental materials such as images, videos, and medical devices may be used to provide respondents with a more accurate understanding of the health states
   - Avoid uncertainty in health states as much as possible
   - Consider advantages and disadvantages of naming the disease in the health state (i.e., the disease label)
   - Format vignettes to maximize comprehension and reduce error in the valuations (e.g., bullet points, large clear font, generous spacing, headings, colors, bolding, shading)
4. Refine the vignettes: The initial draft should be edited and refined based on two sources of information.
   - Clinicians and/or patients should review the draft health states to confirm that they clearly and accurately represent the typical patient experience
   - The vignettes and utility valuation methods should be tested in a pilot study to assess clarity and comprehension of the health states, as well as the number of vignettes each participant can value

greater insight into the patient experience. For example, with some types of chemotherapy, oncology nurses may spend more time with patients than the treating physicians. In some situations, however, clinicians may not be able to report the broad impact of a condition or treatment across all domains of HRQL due to their focus on clinical aspects of disease. If there are areas of disease impact that might be unfamiliar to clinicians, patient interviews may be a useful way to fill these gaps.

A relatively small number of clinicians are required to describe health states focusing on objective content, such as procedures for using medical devices.[17] Two may be sufficient to confirm that vignette descriptions match the typical patient experience. Health states with more subjective content (eg, symptoms, AEs) usually require more clinicians (perhaps 4-8). It may also be necessary to talk to clinicians from multiple specialties. For instance, for vignettes describing diverse AEs associated with antiretroviral treatment, input was gathered from a cardiologist, nephrologist, and several infectious disease specialists.[42] The number of clinicians needed to support a set of health states also depends on the medical condition. For rare conditions, clinicians may not have experience treating patients across the range of severity represented in vignettes.

Clinicians may be interviewed multiple times. The first round of interviews can be conducted to gather information before developing health states, and subsequent discussions can continue throughout health state development until all clinicians agree that the vignettes accurately represent the typical patient experience. When clinicians disagree, a group meeting by teleconference is often helpful for reaching consensus.

An empirical approach is to derive vignette statements from quantitative data such as an outcome measure in a clinical trial.[75-77] For example, 1 study included 2 vignettes representing adults with attention-deficit/hyperactivity disorder categorized as treatment responders or nonresponders.[78] Health state descriptions were adapted from items on patient-completed rating scales (eg, "you have problems organizing tasks and activities"). The 2 health states were differentiated based on the response options most frequently selected by each patient group as indicated by a pooled analysis of clinical trial data (eg, symptoms occurred "once in a while" with "minimal consequences" for responders and "often" with "real consequences" for nonresponders). This empirical support provides evidence that the health states are a reasonable representation of the target population.

A newer method for assessing the patient perspective is to analyze qualitative data from online patient discussion forums.[42] This approach provides unique insight into the patient

perspective expressed outside the research or clinical context. This methodology can efficiently capture rich qualitative data from large patient samples, although results should be interpreted with caution because accuracy of clinical diagnosis is uncertain, and the online discussions may not focus on the issues that are most relevant for vignette development.

When articles reporting vignette-based studies are submitted for publication at peer reviewed journals, reviewers should carefully attend to the sources of evidence used to support the vignette content. If this evidence is not clearly presented, clarification and additions should be requested for inclusion in a revised article. If the evidence is insufficient, the vignettes cannot be trusted as a reasonable representation of the medical condition, and the manuscript should not be published. The types of evidence described above are summarized in Table 2.

Table 2. Suggested information to be included in publications of vignette-based utility estimation studies.

Section	Details
Introduction	• Brief background on the medical condition and its treatment • Justification for using vignette-based methods, including reasons why GPBMs completed by patients would not be sensitive, appropriate, or feasible
Methods	• Description of evidence used to develop the health states. Evidence may include several of the following sources of information: ◦ Citations of relevant published literature ◦ Clinician interviews (specify clinician's experience relevant to the health state descriptions and interview methods) ◦ Patient interviews (specify demographic/clinical characteristics and interview methods) ◦ Caregiver interviews (specify relationship to patient) ◦ Quantitative data (eg, patient-reported outcome measures in clinical trials) ◦ Qualitative coding of social media data such as online patient discussion forums (specify data source and coding methods) • Description of the health states, including domains and formatting • Methods for validating and refining vignettes ◦ Presenting vignettes to experts (eg, clinicians, patients) and making edits based on their feedback ◦ Pilot study in which health states are valued in utility elicitation tasks with the target population, which may be either patients or general population respondents • Utility interview procedures • Population used to elicit utility values (including recruitment and sample size) • Interview setting (eg, in-person individual interviews, group administration, or online utility elicitation) ◦ Introductory tasks (eg, visual analogue scale or ranking of health states) ◦ Order of health state presentation ◦ Utility elicitation procedures: the choices presented to respondents, the ordering of the choices (eg, ping-pong approach), justification for the time horizon (eg, 10 years), intervals between choices (eg, number of years/months for TTO; percentages for standard gamble) ◦ Approach for valuing health states perceived as worse than dead ◦ Plans for addressing logical inconsistencies or unusual patterns of data during the interviews (eg, methods for carefully querying unusual responses to confirm that they represent the respondent's true preference, rather than a mistake) ◦ Scoring for both positive and negative utilities • Statistical analysis procedures including descriptive statistics, utility comparisons, subgroup comparisons, plans for addressing logical inconsistencies, negative utility scores, and/or outliers
Results	• The results that will be presented vary depending on the purpose of the study. At a minimum, mean utilities are typically presented (with SD or 95% confidence intervals). The following results may also be included: ◦ Mean utility difference scores for comparisons between health states ◦ Parameters from regression models of utility scores based on the health states and covariates ◦ Significance testing of differences between health state utility scores ◦ Frequency of differentiation between health states (ie, the percentage of respondents who had different utility scores for a pair of health states) ◦ Frequency of negative utility scores for each health state ◦ Results of introductory tasks (eg, ranking the health states), which can be a useful way to check validity of the utilities ◦ Frequency of logical inconsistencies ◦ Subgroup comparisons (eg, utilities for subgroups categorized based on demographic or clinical variables)
Discussion	• Summary of key preferences • Potential use of the utilities (eg, how might the utilities be included in a model) • Comparisons to relevant utilities derived in previous studies • Limitations of the methodology and the specific vignettes
Supplemental material	• Complete health state text should be provided. If this material is too long to be included in the article text, it may be presented as an appendix or as supplemental material available online. Because any word or phrase in a vignette can have an impact on the resulting utility value, it is important that reviewers, readers, and modelers using the utilities have access to the full vignettes • If formatting is unique, a formatted health state may be presented • Other materials used to help participants understand the vignettes (eg, images used in vignettes, screenshots from videos, or photos of medical devices that were used to clarify health state content)

CUA indicates cost-utility analysis; GPBM, generic preference-based measure; SD, standard deviation; TTO, time trade-off.

3. Draft the Health State Descriptions

The structure of vignettes varies across studies, but there are some general principles that should be considered when drafting vignettes.

Comprehension

Vignettes should be designed to maximize comprehension. It is essential that respondents can understand the health states, recall the content, and identify differences between health states. When vignettes are too long, respondents tend to focus only on a few details because it is difficult to remember all the information. Therefore, vignettes should be as brief as possible. Furthermore, descriptions must be presented in simple language that avoids medical jargon so that they can be understood by almost all respondents. Shorter, simpler health states are easier to comprehend and value accurately in a preference-based task, thus ensuring that the resulting utilities are based on a good understanding of health state content, while minimizing error and logical inconsistencies.

Typical patient experience

A health state vignette cannot represent the full range of patient experiences with any disease or treatment. Instead, vignettes should describe the typical patient experience, and the resulting utility will represent this "midpoint" health state. Therefore, health states should include the most common attributes, while omitting unusual patient experiences that could clutter the vignette and obscure the main points.

Comparability between vignettes

Often, the most important results from a vignette-based study are the differences between health state utilities, which represent differences in preference. Thus, health states should be designed to facilitate comparison between health states with parallel structure and statements to ensure that participants can recognize the differences.

Supplemental materials

Supplemental materials may be used to help respondents understand vignettes. For some medical conditions (eg, dermatologic), images may help clarify health state content. Videos may help clarify observable symptoms or procedures.[17,76,79,80] For health states describing medical devices, interviewers may be able to demonstrate using the devices.[17] For visual acuity, devices have been used to simulate visual impairment.[81] When presenting health states that change over time, a timeline depicting the series of events can add clarity.[74]

Avoid uncertainty

Whenever possible, health states should avoid statements with uncertainty, such as "you may feel fatigued" or "you might require treatment." Respondents' interpretations of these uncertain statements will vary. While some respondents optimistically assume the best possible outcome, others expect more negative outcomes. If participants each make their own unique assumptions when valuing health states, this will increase variability and error, making it difficult to know exactly which health state the utilities represent. Sometimes, it may be necessary to include some uncertainty to reflect the patient experience accurately, such as living with the risk of serious AEs.[42] However, this should be done with caution because any uncertainty interferes with interpretation of results and reduces confidence in utility scores.

Labeling the medical condition

Previous research has examined the effects of naming (ie, labeling) the disease in a health state. There is some evidence that naming the disease can influence utility,[82] although other studies have reported that the disease label did not affect results.[83,84] Some diseases such as cancer or human immunodeficiency virus may be associated with preconceptions, fear, stigma, or bias. In these situations, it may be important to omit the label. In other studies, naming the disease may help ensure health states are clear and unambiguous. Therefore, when designing vignettes, researchers should consider the advantages and disadvantages of including the label.

Formatting

Careful formatting can help respondents understand the health states and reduce error in the valuations. Vignettes are often presented as a series of individual cards or pages that can be ordered by the respondents (Fig. 2). Bullet point lists are easier to read and comprehend than long paragraphs. Font should be clear and large with sufficient space between bullets to maximize readability. Different colored borders for each vignette can help respondents distinguish between a set of health states. Descriptors should be grouped according to concept, and headings for each category can be provided to help respondents understand the organization of the concepts (eg, symptoms, impact, treatment, AEs). Background colors (perhaps light gray or yellow) can be used to show that specific sections either do or do not vary across a set of health states. Differences between vignettes can be underlined or bolded to help respondents recognize and remember them. However, the use of too much color and emphasis can be distracting and confusing, and the vignette formatting should be assessed in a pilot study.

4. Refine the Vignettes

After the initial draft, health states require editing and refining based on 2 sources of information. First, clinicians and/or patients should review the draft health states so that edits can be made based on their feedback. Generally, health states should not be considered final until all these experts agree that they clearly and accurately represent the typical patient experience. If experts disagree, a discussion among multiple clinicians may be arranged to reach consensus.

Second, vignettes and utility valuation methods should be tested in a pilot study to ensure that respondents understand the health states and can distinguish between them in a logical way. Health states can be edited based on respondents' feedback. A pilot study is also useful for determining how many health states are feasible. If it appears that participants cannot provide reliable valuations for a set of health states because there are too many, each participant can be randomly assigned to value a subset, but this strategy reduces the sample size for each vignette (unless the sample size is increased to compensate). If the pilot is conducted in multiple phases, health states can be edited throughout so that the final pilot participants value the final set of health states.

The pilot sample size depends on the complexity of the health states. A sample of 20 respondents is usually sufficient, but fewer may be enough to reach saturation (ie, the point when no new information is provided) if the vignettes are straightforward. More participants might be needed if health states are complicated or if the researchers are uncertain about the optimal utility assessment method. After the pilot, the vignettes should be ready for use in a larger valuation study.

Figure 2. Example of a formatted health state vignette.*

A	
Description†	• You have **migraine**.‡ This is an unpredictable disorder that causes disabling headaches and other associated symptoms. • You are treated with a **medication** that reduces the number and duration of migraine episodes. • Because of the treatment, you have fewer headaches.
Treatment§	• You are treated with **one injection every 4 weeks**. • You give yourself this injection **at home**. • You can inject yourself in the thigh or abdomen.
Symptoms‖	• You now have migraine headaches **5 to 8 days each month**. Each headache lasts about **2 to 6 hours**. • At the beginning of each episode, you feel tired and you notice that you have neck discomfort. • Each episode includes a very **painful headache**, usually on one side of your head. The pain is severe and throbbing, and it becomes worse with movement. • During each episode, it is **hard for you to concentrate**. You feel like you have "brain fog." • During many of these episodes, you feel like you are going to be sick (nausea), and you feel uncomfortably **sensitive to light and sound**. • After each migraine episode, you feel **tired and worn out**.
Impact¶	• On days with a migraine, it is **difficult for you to perform everyday tasks.** • For example, when you are affected by migraines, it is difficult to concentrate and be productive at home, work, or school. • If you have children, it is difficult to care for them on days with a migraine. • When you have a migraine, you would prefer to stay at home.

* This vignette, called "health state A," was used in a published study.[16] Several aspects of the formatting were designed to help respondents understand the health states and the differences between health states. For example, each health state had different colored borders, and descriptions were presented in short bullet points with space between each bullet to maximize readability.

† Descriptors were grouped with headings to help respondents understand the organization of the concepts (e.g., description, treatment, symptoms…).

‡ Health states in this study included the name of the medical condition (migraine) because it was expected that participants would recognize migraine based on the symptoms. Therefore, omitting this label could have raised questions or caused confusion. For some conditions that may be associated with biased preconceptions, such as cancer or HIV, it is often preferable to omit the label to avoid bias.

§ The purpose of this set of health states was to evaluate preferences for various treatment administration options (i.e., to estimate treatment process utilities). The "Treatment" section had a shaded yellow background to indicate that this section varied across health states while the other sections remained constant. Differences between vignettes can also be underlined or bolded to help respondents recognize and remember them.

‖ Symptoms were described based on interviews with clinicians who reported the language patients commonly use to describe typical migraine symptoms. These symptom descriptions were also supported by published literature.

¶ Descriptions of impact are included so that migraine symptoms and treatment can be interpreted in the context of overall functioning, including impact on usual activities and social functioning.

C. Valuing Vignettes

After developing the vignettes, they are valued in preference elicitation tasks, most commonly TTO or standard gamble, to estimate a utility for each health state.[85-88] If necessary, aspects of the utility assessment methods can be varied (eg, the TTO time horizon) to ensure that the methods are appropriate for the health states and sufficiently sensitive to detect true differences in preference. When determining valuation methods for a vignette study, it is useful to consider comparability with GPBMs preferred by HTA authorities. For example, if utilities will be used in a NICE submission, vignettes can be valued using TTO methods similar to those used to derive scoring tariffs for the EQ-5D (3L or 5L).[89]

Whereas valuation studies for GPBMs are conducted to derive a scoring function, the primary results of vignette studies are usually the mean health state utilities. Regression models may also be run to understand the influence of each health state and relevant covariates on utility.[18,39,44,90] The analysis approach should be specified a priori, including methods for addressing logical inconsistencies, outliers, and negative utility scores. To help readers interpret findings, publications should include all details that modelers and reviewers would need to evaluate the utilities (Table 2), including justification for using the vignette-based approach.

D. Use of Vignette-Based Utilities in Models

Vignette-based utilities may be used like other utilities in CUAs.[68] Modelers can use the actual utility value (eg, 0.80 on the utility scale anchored to 0 and 1), but it is also common to use vignettes to identify utility difference scores for adjusting utilities from a standardized instrument. For example, a recently published model used an EQ-5D value of 0.785 for type 2 diabetes as a baseline utility, but added a utility benefit of 0.03 for patients using a new glucose monitoring approach.[91] The difference score of 0.03 was estimated in a vignette-based study.[17] To avoid double-counting the utility impact of an attribute when using this approach, it is important to consider whether the attribute represented in the vignettes also has an impact on the GPBM utility.

One cautious approach is to apply these vignette-based utility adjustments in sensitivity analyses.[68] A CUA can first be run without the adjustments, yielding a base case incremental cost-effectiveness ratio. Then, the CUA can be re-run as a sensitivity analysis with the vignette-based utility adjustments, yielding a different incremental cost-effectiveness ratio. With this approach, HTA reviewers can consider results with and without the vignette utilities.

E. Limitations of Vignette Methods

Before conducting a vignette study or using vignette-based utilities in a CUA, researchers must consider the limitations. First, although vignettes may be rigorously developed based on the best available evidence, the utilities are not directly provided by patients living in the health states. Therefore, the utilities represent preferences for the vignette, which can differ from the health status of actual patients with the condition. While a vignette-based utility may be a useful approximation of patient HRQL, consistency with utilities generated using preference-based measures with patients is uncertain.

Second, the validity of the utilities depends on the accuracy and level of detail of the health state descriptions, which cannot include all possible aspects of the patient experience. Even a well-developed vignette could inadvertently omit details that are important to some patients. Third, because a vignette cannot represent the full range of patient experiences within a health state, the utilities may underestimate the variability associated with most medical conditions.

Fourth, vignette-based methods are not standardized, and procedures for developing and valuing vignettes vary across studies. There is also no standardization regarding the content of a health state description. If vignettes focus on a specific treatment without providing broader context of the medical condition and HRQL, respondents may overestimate the importance of minor attributes without considering other aspects of health. To minimize these focusing effects and increase comparability across studies, vignettes should include broader aspects of HRQL (eg, functioning, usual activities).

Finally, vignettes can lead to biased responses if they emphasize some issues while downplaying others. Therefore, when interpreting results of vignette studies or using the resulting utilities in a CUA, it is important to review the content of the vignettes to ensure that they provide an accurate and unbiased description of the health state. The best way to avoid these limitations is to consider modeling needs early in a drug development program and include a GPBM in clinical trials to gather utilities from patients.[69]

Conclusion

Despite HTA agency preferences for utilities derived from GPBMs completed by patients, there will always be new medical treatments with outcomes, treatment processes, or AEs that could affect quality of life but cannot be captured by standardized instruments. When patient-completed preference-based measures are not feasible or appropriate for obtaining utilities needed for a CUA, a vignette-based approach may be the only available option. Like all inputs in a CUA, vignette-based utilities can affect model results, which inform subsequent decision making and healthcare resource allocation. Therefore, vignette utility studies must be well designed, carefully conducted, clearly reported, and interpreted with appropriate caution.

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Author Affiliations: Evidera, Patient-Centered Research Group, Bethesda, MD, USA (Matza, Stewart); Acaster Lloyd Consulting, London, England, UK (Lloyd); School of Health and Related Research, University of Sheffield, Sheffield, England, UK (Rowen, Brazier).

Correspondence: Louis S. Matza, PhD, Evidera, 7101 Wisconsin Ave, Suite 1400, Bethesda, MD, USA 20814. Email: louis.matza@evidera.com

Author Contributions: *Concept and design*: Matza, Stewart, Lloyd, Brazier
Acquisition of data: Matza
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