Olina Efthymiadou, Jean Mossman and Panos Kanavos

Health related quality of life aspects not captured by EQ-5D-5L: results from an international survey of patients

Article (Accepted version) (Refereed)

Original citation:
Efthymiadou, Olina and Mossman, Jean and Kanavos, Panos (2018) Health related quality of life aspects not captured by EQ-5D-5L: results from an international survey of patients. Health Policy. ISSN 0168-8510

DOI: https://doi.org/10.1016/j.healthpol.2018.12.003

Health related quality of life aspects not captured by EQ-5D-5L: Results from an international survey of patients

Abstract

BACKGROUND: In this paper we discuss and present evidence on whether a generic Health Related Quality of Life (HRQoL) measurement tool, the EQ-5D-5L, captures the dimensions of quality of life (QoL) which patients consider significant. **METHODS:** An online survey, of individuals with a chronic condition, mainly breast cancer (BC), blood cancers (BLC), rheumatoid arthritis (RA), asthma, and rare diseases (RD) was conducted to collect data on HRQoL and important QoL aspects that respondents thought were not captured by the EQ-5D-5L. Patient organisations across 47 countries were invited to voluntarily share the survey tool with their membership network. **RESULTS:** 767 responses from 38 countries showed that important QoL aspects were not captured by EQ-5D-5L for 51% of respondents, including fatigue (19%) and medication side effects (12%), among others. Fatigue (17%) was also the most commonly reported QoL aspect that changed over the course of patients' illness, suggesting that the current version of the EQ-5D-5L might miss capturing significant clinical changes in important QoL domains. **CONCLUSIONS:** Utilisation of the EQ-5D-5L in HRQoL measurement raises inconsistencies in capturing QoL attributes and changes in disease-specific patient populations. Further research is needed to clarify the extent to which other generic HRQoL measurement tools capture the aspects of health that really matter for patients.

Keywords

QoL utilities; Patient preferences; QALY; Health Technology Assessment; EQ-5D-5L; Cost Utility Analysis.

Highlights

1. EQ-5D-5L didn’t capture key QoL dimensions for more than half of the sample.
2. Several QoL aspects, notably fatigue, were identified as overlooked by EQ-5D-5L.
3. Around 60% of patients reported changes on key QoL aspects during their illness.
4. It is unknown if other generic HRQoL measurement tools face the same challenges.

Background

Health Technology Assessment (HTA) is used extensively by health care systems globally, to inform resource allocation decisions around the uptake of new health technologies [1]. In order to be efficient, HTA must harmonize the interests of the general population, healthcare systems and individual patient groups. Essentially, HTA should recommend the uptake of cost-effective technologies, which have a substantial benefit to patients at an affordable cost, while balancing societal preferences [2]. Since patients are the end users of medical technologies it is imperative that their experiences play a significant role in HTA decision-making. This is usually achieved through relevant data captured in clinical trials, which feed into HTA, while in certain cases, for example when in-depth understanding about the value and impact of a specific technology in patients' lives is required, the inclusion of primary patient testimonies provides additional means for patient involvement in the HTA process [3, 4], Despite a universal desire for a collaborative approach to healthcare decision-making, with patient involvement being an important priority, the input of patients, their caregivers and associated organizations towards HTA decision-making remains inadequate [4]. Evidence shows that only around half of the HTA bodies worldwide have reported the use of direct patient/caregiver involvement within any aspect of their processes [5]. Indirect patient involvement (e.g. through secondary evidence on patients' Quality of Life (QoL)) is very often based on the use of evidence generated through generic Health Related Quality of Life (HRQoL) measurement tools, which have often been debated for their insufficiency in capturing key aspects of patients' health status [3,6,7]. Health utilities can be measured indirectly using multidimensional, multi-attribute HRQoL questionnaires such as the Health Utilities Index 2 and 3 (HUI2 and HUI3), the Short Form 6D (SF-6D) and the EuroQol (EQ-5D) [8]. Essentially, HRQoL data derived from patient populations help to generate Quality Adjusted Life Years (QALYs), a health utility metric which reflects health outcomes related to a treatment benefit and hence, serves as a baseline from which to tailor interventions, pharmacological or otherwise, and assess their comparative and cost effectiveness, both in the clinical trial setting and in routine care [17].

Whilst these measures are all generic and not disease-specific, they differ considerably in terms of their content [9]. Even though EQ-5D and SF-6D are both being commonly used in economic evaluations [10], EQ-5D has become the most widespread generic measure of health utility used for economic evaluation in Europe [10] and internationally [11]. EQ-5D and its 5-level follow-on (EQ-5D-5L) have been certified in many countries worldwide [12, 13] and advocated for use in measuring the performance of a national health system [14], the real life effectiveness of interventions, and patients' preferences [15].

The EQ-5D-5L assesses areas of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and identifies a total of 3125 (=5^5) possible health states, taking values from 0 (death) to 1 (perfect health) and therefore, presents with the fewest domains when compared to the other preference-based measures [8, 16].

By imposing pre-defined domains on HRQoL measurement, this tool is also believed to lack dimensions of HRQL that may be impacted by chronic diseases (i.e. dexterity and social functioning); therefore, it raises questions as to the extent to which it represents the pragmatic QoL of individual patients or groups of patients [3, 8, 17]. Inevitably, unmeasured aspects with a potentially significant impact on an individual's QoL encourage inaccuracies in HRQoL measurements and often result in diverse Health State Utility Values (HSUVs) being obtained by different instruments depending on the dimensions that each tool measures [10].

An additional limitation of EQ-5D-5L is its limited responsiveness to clinical changes over the course of a treatment [3]. Health state improvement/deterioration, whether this arises as a consequence of treatment or of disease progression itself, should be reflected in the EQ-5D-5L score in order to provide a reliable calculation of the QALYs gained/lost from a treatment. Since reimbursement decisions in many countries are primarily based on the cost/QALY metric, inaccurate QALY estimates could lead to resource allocation decisions that are not representative of the true benefit of an intervention.

If coverage decisions are to reflect what matters to the users of a specific technology, their views should be embedded in the decision-making process and this could be achieved by capturing their perspective in a suitable utility measure. Given the widespread use of EQ-5D-5L in HTA internationally, our study focused specifically on this tool, aiming to determine the perspective of individuals suffering from a variety of chronic conditions on how well the EQ-5D-5L reflected their experience of illness.

Methods

Sample and Research design

We conducted a web-based survey of an international patient population. Our sample comprised adult individuals diagnosed with at least one chronic condition. Participants were identified through a network of patients and patient associations' representatives, held by the Medical Technology Research Group at the London School of Economics (LSE).

The survey was based on a multidimensional questionnaire comprising four sections, namely; a) patient demographic information and clinically relevant characteristics such as years since diagnosis and satisfaction with treatment received, b) HRQoL, measured with the EQ-5D-5L, so that patients could subsequently reflect on what was not covered by the tool c) respondents' views about important QoL aspects that they felt EQ-5D-5L didn't capture and d) aspects of illness that changed during the course of patients' illness, as a proxy of to measuring the representativeness of EQ-5D-5L to clinical change.

Questionnaires were made available in six languages and 320 patient associations across 47 countries, primarily from Europe (308 - whether at national or supra-national level) were invited via e-mail to voluntarily share the questionnaire with their network of patients via e-mail, blogs and social media accounts. The invitation to participate in the survey was sent to hundreds of patient organisations internationally, equally representing a variety of chronic disease patients, including Cancer (e.g. European Cancer Patient Coalition - ECPC), Breast Cancer - BC (e.g. EuropaDonna), Blood Cancer - BLC (i.e. Myeloma Patients Europe - MPE), Myelodysplastic Syndrome (MDS) (e.g. MDS-UK), Rheumatoid Arthritis - RA (e.g. European League Against Rheumatism - EULAR), Asthma (e.g. Asthma UK) and Rare Diseases - RD (e.g. Rare Connect), among others. A detailed list of the chronic diseases represented in this study is provided in the Appendix for clarification (Appendix, Table 1).

In order to ensure anonymity, responses had no identification information. All patients were informed about the study objectives and data confidentiality procedures in place and were asked to provide online written informed consent, to indicate their understanding of the study conditions and their agreement to participate. The study protocol was submitted to the LSE Research Ethics Committee and received an exemption.

Preceding the actual survey questions, an online information sheet described the objectives of the survey, data confidentiality policies and provided individuals with a brief description of the EQ-5D-5L tool and its utilisation in HRQoL measurement. The survey was hosted online between June and August 2015 on Qualtrics® software under an LSE-verified account. The IBM Statistical Package for Social Sciences (SPSS) version 21 was used to generate descriptive statistics (mean, median and standard deviation) and assess statistical significance of differences between groups.

Information and main variables of interest

In order to gauge the extent to which EQ-5D adequately captures the aspects that impact on patients' wellbeing the survey specifically asked patients to complete the EQ-5D-5L questionnaire and subsequently, to respond to the following questions i) "Are there any aspects of your illness, which have had a big impact on your health, that were not captured by the EQ-5D-5L" questionnaire which you completed previously – No/Yes, ii) "If yes, please tell us what they are", iii) "Have the aspects of your illness, which have had a big impact on your health, changed over the course of your illness?" – No/Yes, iv) "If yes, please tell us what those changes were and how they have impacted your life".

Results

Completion rate and sample size

Based on the invitations to 320 patient associations, a total of 1,031 surveys were initiated from all 47 countries and 767 surveys were completed from 38 countries (completion rate of 74%), namely Armenia (n=1), Australia (n=5), Austria (n=1), Belgium (n=9), Bulgaria (n=2), Canada (n=2), Croatia (n=12), Cyprus (n=32), Czech Republic (n=1), Denmark (n=37), Estonia (n=5), France (n=39), Germany (n=10), Gibraltar (n=1), Greece (n=55), Hungary (n=1), Ireland (n=7), Israel (n=2), Italy (n=6), Japan (n=1), Lithuania (n=2), F.Y.R.O.M (n=1), Malaysia (n=1), Malta (n=3), Moldova (n=1), Netherlands (n=33), Norway (n=3), Poland (n=3), Portugal (n=9), Romania (n=34), Serbia (n=4), Slovakia (n=4), Slovenia (n=15), Spain (n=10), Sweden (n=3), Switzerland (n=3), UK (n=400) and USA (n=9). 122 disease diagnoses were reported in total. Cancer was the most common diagnosis (n=328, 48% of study sample), among which BC (n=180) and rare cancers (n=48) were dominant (23.5% and 6.2% of study sample respectively). Rare cancers mainly comprised blood cancer (BLC) diagnoses (n=31, 4% of study sample). Rare disease (RD) diagnoses (n=140, 18.2%), RA (n=53, 6.9%) and Asthma (n=24, 3.1%) were also represented (Appendix, Table 1).

Sample demographic and HRQoL characteristics

Average patient age was 50 (±14) years, the majority was females (77%), married/cohabiting (67%) and employed (40.7%). Average patient HSUV was 0.62 (±0.27), translating to an average utility loss of 28%, when compared to the general population in the study countries. Among the main disease groups of the study, the lowest average HSUV was reported by RD and RA patient groups (40% and 27% utility loss respectively), whereas the highest HSUV (i.e. 0.73, ±0.16) was observed for the BLC patient group.

Aspects not captured by EQ-5D-5L

Our analysis showed that 51% (n=359) of all patients who responded (n=705) to the question; "which aspects of their illness had a big impact on their health, that were not captured by the EQ-5D-5L", considered that the tool didn't capture all the important wellbeing aspects that added a significant burden to their HRQoL (Figure 1).

<Figure 1 about here>

9.5% (n=34) of the above patients who reported that the tool didn't capture all the important wellbeing aspects that added a significant burden to their HRQoL (n=359) did not provide a text response to describe the aspects of their illness that were not captured by the EQ-5D-5L. By virtue of the free text responses available (n=325), it was highlighted that the most commonly reported wellbeing aspect not captured by the EQ-5D-5L was that of fatigue (19% of respondents who specified such aspects). Following were medication side effects (SEs) (12%) (i.e. "*Tamoxifen caused depression and lack of libido*", "*Hair loss*"), presence of other co-morbid/long-term conditions (9.5%) (i.e. "*While 'cured' of AML I have a compromised immune system and I am prone to chest infections. I have mild Graft-versus-host (GVH) disease affecting my eyes and acute arthritic attacks*"), maintenance of relationships and social life (6.5%), issues with clinicians and social care received (6.2%), cognitive impairment (4.3%), sleep deprivation (4.3%), maintenance of family relationships (3.7%), worries/fear about the future (3.7%), work limitation (3.7%) and financial problems (2%) (Table 1).

Other, less common aspects included; loss of confidence/self-esteem (1.9%) (i.e. "*Self-image, confidence*", "*The view I have of myself*"), sexual dysfunction (1.8%) (i.e. "*Sexual discomfort*", "*Vulvar fragility*"), inability to exercise (1.5%), emotional distress (1.2%), inability to travel (<1%) and loss of senses; eyesight and hearing (<1%). Amongst the above, "loss of confidence/self-esteem" and "sexual dysfunction" were predominantly reported by BC patients (6% and 5% respectively). Finally, nearly 4% did not understand or had difficulty in understanding what the EQ-5D-5L tool was (i.e. "*I have not done an EQ-5D-5L*", "*I don't know what EQ-5D-5L is*").

<Table 1 about here>

6.2% (n=20) of those who provided a free text response (n=325), primarily RD, BC and RA patients, reported that an important aspect of their wellbeing is related to issues experienced with the medical and social care received (Table 1); issues were raised that medical staff were not necessarily knowledgeable on providing the tailored care and treatment that RDs require, or that often, the way BC patients were informed about their diagnosis was felt to be appalling. Similarly, delayed diagnosis and access to treatment was an aspect that impacted greatly on the wellbeing of RA, diabetes and Multiple Sclerosis (MS) patients. In addition, 5.2% of patients did not specify a health aspect that was not captured by EQ-5D-5L but instead, they provided comments highlighting the tool's inability to capture daily variations of their wellbeing and QoL (Appendix, Table 3). Finally, 9.8% of individuals reported specific aspects of domains that were actually covered by the EQ-5D-5L, including anxiety/depression (4%), pain (3%) and mobility (1%), indicating that either they did not understand fully the items described by the EQ-5D-5L or that the EQ-5D-5L domains were of relevance to their wellbeing but they were not addressed adequately (i.e. did not fit the patients´ understanding of the individual items and their respective severity levels as phrased by the tool).

Aspects that changed over the course of the disease

57% (n=401) of all patients who responded (n=705) consider that the aspects of their illness that have a big impact on their health have changed over the course of their disease (Figure 2).

<Figure 2 about here>

Excluding 7.7% (n = 31 out of 401) of respondents who did not provide a free text response on "what these changes were and how they had impacted their life", for those who specified such changes (n=370), the most commonly reported were related to the following aspects; fatigue (17%), pain/discomfort (14%), mobility (12.4%), SEs (11.4%), treatment and/or healthcare received (n=26, 7%), work limitation (6.5%), usual activities (4.3%), maintenance of relationships and social life (3.8%), inability to exercise (3%), development of other co-morbid/long-term conditions (3%), anxiety/depression (2.7%), and cognitive impairment (2.7%) (Table 2). Other less common aspects that changed included fear for relapse/ for future; (2.4%), sleep deprivation (2.1%), sexual dysfunction (1.3%), financial problems (1%), loss of confidence/self-esteem (1%), maintenance of family relationships (1%), appearance/bodily image (<1%), loss of senses; eyesight and hearing (<1%), and self-care (<1%). The aspect of "Fear for relapse" was primarily reported by cancer patients; i.e. *"Anxiety for relapse" (BC patient), "Ongoing worries about whether the cancer may come back," (BC patient), "Worry of recurrence with each chest infection" (Lung cancer patient).*

<Table 2 about here>

Discussion

We observed that EQ-5D-5L missed important health aspects in approximately 51% of an international, chronically ill population, although this percentage fluctuated according to disease area

Overall, there were 17 additional QoL aspects identified, as being important but not represented by the EQ-5D-5L. In this context, the most commonly reported missing aspect (as reported by 19% of the entire sample and 24% of the cancer sample) was that of fatigue and loss of energy. A Swiss study [18] using a general adult population to elicit QoL preferences, reported on five additional, hypothetical EQ-5D-5L dimensions. Similarly to our results, the most frequent source of complaints was with regards to fatigue and lack of energy, although complaints regarding fatigue were higher (52.5% of complaints) in the Swiss study, in comparison to our study, possibly due to the smaller sample size used in the former.

Comparably, a QoL survey on cancer patients showed that 43% of patients agreed or strongly agreed with the statement “I always feel tired” [19]. Fatigue has long been recognised as an important candidate for inclusion in the development of QoL valuation tools [20], as the role it plays in the worsening of the physical, mental, emotional and social aspects of QoL has been well documented [21-23]. It is associated with multidimensional consequences, ranging from functional impairment to interferences with employment, daily activities and relationships [23]. Specifically in cancer, fatigue has been linked to increased depression, anxiety, mood disturbances and negative impact on the family’s financial situation [24, 25]. Similarly, an explanatory study on EQ-5D bolt-on items (i.e. disease-relevant items, supplementary to the EQ-5D-5L, for measuring HRQL in patient groups in which a generic measure has been shown to miss important dimensions) representing vision/hearing impairment and tiredness demonstrated that all bolt-ons significantly impacted on EQ-5D valuations, although the vision bolt-on appeared to be the most influential compared to hearing and fatigue [11]. Even though fatigue is clearly important to patients, its potential as a bolt-on item to the existing EQ-5D has been met with resistance [26]. Evidence has shown that when an experimental 6 domain version of the EuroQol questionnaire was tested in a pilot study, the impact that fatigue had on valuations was so small that it was deemed unnecessary to investigate further the development of a tool that adds fatigue as an additional domain [27]. Clearly, our findings are in direct contradiction with the above and this can be explained by using different target populations in each case.

Nevertheless, the issue of fatigue is complex. It is the aspect of illness which many patients with chronic diseases report as having the highest impact on their daily living. Fatigue can be related to both the disease and its treatment, and impacts a person's wellbeing in ways that are different from their inability to carry out normal activities. A study of cancer patients found that fatigue affects more patients for more time than any other symptom and is regarded by patients as being more important than either pain or nausea/vomiting [28].

Furthermore, we demonstrated that another potential shortcoming of EQ-5D-5L relates to its ability to capture changes in patient wellbeing over time. Evidence from the literature shows that there are issues with the use of the tool in situations where the natural history of the disease may vary, in the form of relapses and remissions, with specific evidence from conditions such as asthma, diabetes and MS [27]. Our findings are supportive of the literature, with nearly 6% of all patients across various conditions, including asthma, BC and RD questioning EQ-5D-5L's ability to capture variations in patient wellbeing over time, which impacted on their QoL. Nevertheless, when interpreting these results it is important to keep in mind that measuring HRQoL consistently during periods of disease exacerbation may not be feasible, as such periods are usually short-lived.

In addition, variations over time arising from a fear of relapse may have already been captured in other aspects of the tool [20], under domains such as anxiety. However, our study findings did not support the above, as nearly 5% of those who specified important wellbeing changes (n=370), predominantly cancer patients, stated that anxiety and fear for the future, specifically related to the 'threat' of a relapse or a metastasis, were not captured by the EQ-5D-5L. In a similar context, we could infer that even though the issues experienced by 6.2% of respondents with medical and social care received could have indeed aggravated their anxiety and/or depression levels, their overall impact on patients' QoL would have not necessarily been captured by the respective EQ-5D-5L domain of "anxiety/depression".

Additionally, our results showed that nearly 10% of individuals reported as "important aspects not captured by the EQ-5D-5L", aspects that were actually covered by the instrument, although most likely not with the specificity, or at the severity level respondents expected. This discrepancy raises the question of whether this was a result of the 'framing' of the health states and severity levels within the questionnaire [20] or a result of a misinterpretation of the domains and severity levels described. One can assume that indeed some EQ-5D items do not address patient-specific concerns adequately (i.e. they did not capture the level of severity that respondents expected).

Equally, it is possible that this may have been due to misinterpretation of the instrument descriptions leading to an over-estimation of those who thought EQ-5D didn't capture important health aspects; in this case, it would likely also have more serious implications and should be examined further [35].

Another aspect not captured by the EQ-5D-5L, mostly specific to cancer patients, included medication SEs. The weakness of the EQ-5D to capture problems arising due to adverse events has been documented elsewhere [27]. This is partly supported by our results, showing that 12% of those providing a free text response (n=325) felt that a domain relating to medication SEs was lacking. Specific concerns have been raised with respect to cancer treatment SEs as, very often the adverse reaction profiles of several therapies is characterized by fatigue/energy or nausea and as such, provides evidence for the importance of including the respective domains in an HRQoL measurement tool [27]. The above also relates to concerns that have been expressed elsewhere regarding the ability of the EQ-5D tool to pick up on subtle but important consequences of cancer, such as sexual dysfunction and confidence with self-image [3, 26, 29].

In support of our findings, previous studies have demonstrated the potential that EQ-5D bolt-on items have in enhancing the validity and responsiveness of the tool [7, 11, 30, 31]. However, as the impact of the bolt-ons depends on the severity of the bolt-on item and the severity of the state to which they are added, this raises questions as to whether future bolt-ons need to be valued alongside the EQ-5D descriptions each time and as to the financial and practical challenges that come with increasing the number of health states included in a generic tool such as the EQ-5D-5L.

Ultimately, we propose an alternative approach whereby a small subset of alternative health dimensions, specific to a particular subgroup of the population, are derived that could be used to sufficiently explain a large proportion of the variation in patient health utility. Different subsets of health dimensions could be employed depending on the disease at hand. The findings from this study demonstrate that an adaptive approach to EQ-5D-5L may be needed to capture disease-specific elements; alternatively, EQ-5D-5L could be used to add a generic element to a disease-specific tool thus capturing a significant part of unexplained heterogeneity that we observed in this study. A similar approach was used in one of the early studies in the field which included a generic bolt-on item with a condition-specific measure of HRQoL [31].

This discussion unavoidably links with the use of patient reported outcomes in drawing regulatory conclusions regarding treatment effects. Although there is debate around the use of such data in clinical trials [32, 33] and acceptance of their role in regulatory decision-making [34], our study has shown that their usefulness stretches beyond estimates of patient perception of therapy side effects. The results of this study may, therefore, have important implications for a number of steps in data generation processes that lead to value assessments of new medical technologies in different settings: first, the kind of data that we ought to capture in clinical trials, second, how to reflect the broad patient population's perspective and, third, what should regulatory bodies consider. Come what may, by confirming results from comparative efforts elsewhere, the present study showed that a more coordinated or broadly-based approach is needed and that leaving things as they are – the do-nothing option – does not appear to be acceptable to half the patient population surveyed.

Study Limitations

We believe that our analysis can prove valuable for improvements in future QoL research and HTA processes. However, we acknowledge that certain methodological limitations have hindered the robustness of our findings. .

The first limitation relates to sampling issues. Due to time constraints, a convenience sample was drawn, which mostly comprised European-based patients. As such, 71% of participating countries contributed less than 10 responses and the majority of responses were limited to BC, RA and RD patients. In obtaining the responses for this study, we relied on the voluntary involvement of patient organisations and since some of them have inherently generated greater participation in the survey, a greater sample size for the respective disease groups was achieved compared to others. Additionally, for logistic reasons the data collection was for a limited period only and this may have also impacted the number of organisations that responded and the diseases that are represented. Therefore, besides the sufficiently large overall sample size, our results might still not be representative of the true international population of chronically ill individuals.

Furthermore, the use of a web-survey raises issues related to the interpretation of the survey questions by the respondents, the levels of understanding of the different EQ-5D-5L domains and the respective severity levels described. Therefore, the results presented in this paper should be interpreted with caution. Finally, the results presented here refer to EQ-5D-5L only and as such cannot be generalised to other generic health state utility measures. Future research may employ a similar approach to assess the validity and/or responsiveness of other generic measures.

Conclusion

QoL is an important measure of disease burden, as unlike other measures, it takes into account patients' subjective perceptions of wellbeing, treatment and overall QoL satisfaction. Understanding the factors which may reduce QoL outcomes is therefore important, for the implementation of more efficient disease management programmes, but also to pinpoint disease manifestations that may have previously been overlooked and accordingly, direct the development of new therapies. It is therefore necessary to have appropriate tools in place to collect such data. However, due to practical issues, currently used HRQoL measurement tools typically focus only on a limited number of health dimensions and are thus believed to measure general health status rather than capturing QoL shaped by a unique combination of different important aspects for each individual.

Despite its limitations, our study demonstrated that in a self-selected population, one of the most widely used QoL measurement tool, the EQ-5D-5L, indeed does not capture all aspects of health state that matter to patients. Inevitably, unmeasured health related aspects perceived to have a significant impact on an individual's QoL generate inaccuracies in HRQoL measurements. Since reimbursement decisions in many countries are primarily based on the cost/QALY paradigm, utilization of inaccurate QALY estimates would imply that economic evaluations and consequently allocation decisions are not representative of the true benefit of an intervention.

Consequently, the issues discussed in this study should guide further research, focused on clarifying the extent to which EQ-5D and other generic HRQoL measurement tools capture the aspects of health that really matter for patients, but more importantly, also the extent to which generic HRQoL measures, including the EQ-5D could be improved in order to capture such aspects.

References

1. Sorenson C, Drummond M, Kanavos P. Ensuring value for money in health care: The role of health technology assessment in the European Union. London: European Observatory on European Health Systems and Policies; 2008.
2. Drummond MF, Wilson DA, Kanavos P, et al. Assessing the economic challenges posed by orphan drugs. Int J Technol Assess Health Care. 2007;23:36-42.
3. Tordrup D, Mossman J, Kanavos P. Responsiveness of the EQ-5D to clinical change: is the patient experience adequately represented? Int J Technol Assess Health Care. 2014 Jan;30(1):10-19.
4. Facey K, Boivin A, Gracia J, et al. Patients' perspectives in health tech- nology assessment: A route to robust evidence and fair deliberation. Int J Technol Assess Health Care. 2010;26:334-340.
5. INAHTA. Involvement of consumers in the HTA activities of INAHTA members. 2011. http://www.inahta.org/News/Survey-Report— Involvement-of-consumers-in-the-HTA-activities-of-INAHTA- members-/ (accessed October 28, 2015).
6. Dolan P. How does NICE value health? BMJ 2009;339:b2577
7. Pietersma S, de Vries M, van den Akker-van Marle ME. Domains of quality of life: results of a three-stage Delphi consensus procedure among patients, family of patients, clinicians, scientists and the general public. Quality of Life Research. 2014;23(5):1543-1556.
8. Marra CA, Woolcott JC, Kopec JA, Shojania K, Offer R, Brazier JE, Esdaile JM, Anis AH.A comparison of generic, indirect utility measures (the HUI2, HUI3, SF-6D, and the EQ-5D) and disease-specific instruments (the RAQoL and the HAQ) in rheumatoid arthritis. Soc Sci Med. 2005 Apr;60(7):1571-82.
9. Brazier & Rowen 2011. NICEDSU TECHNICALSUPPORT DOCUMENT 11:ALTERNATIVES TO EQ-5D FOR GENERATING HEALTH STATE UTILITY VALUES. REPORT BY THE DECISION SUPPORT UNIT. March 2011. http://www.nicedsu.org.uk/TSD11%20Alternatives%20to%20EQ-5D_final.pdf
10. Brazier J, Roberts J, Tsuchiya A, Busschbach J. A comparison of the EQ-5D and SF-6D across seven patient groups. Health Econ. 2004 Sep;13(9):873-84.
11. Longworth L, Yang Y, Young T, Mulhern B, Hernández Alava M, Mukuria C, Rowen D, Tosh J, Tsuchiya A, Evans P, Devianee Keetharuth A, Brazier J.Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. Health Technol Assess. 2014 Feb;18(9):1-224.
12. Jones KH, Ford DV, Jones PA, John A, Middleton RM, Lockhart-Jones H, Peng J, Osborne LA, Noble JG. How people with multiple sclerosis rate their quality of life: an EQ-5D survey via the UK MS register. PLoS One. 2013 Jun 11;8(6)
13. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, Swinburn P, Busschbach J. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013 Sep;22(7):1717-27.
14. Parkin et al., 2008; Office for Health Economics. Report of the OHE Commission on NHS outcomes, performance and productivity. 2008; London: Office for Health Economics.
15. Carr AJ, Higginson IJ. Are quality of life measures patient centred? BMJ : British Medical Journal. 2001;322(7298):1357-1360.

16. Brooks R., Robin R., de Charro F.(Eds.), The measurement and valuation of health status using EQ-5D: a European perspective (evidence from the EuroQoL BIOMED research programme), Kluwer Academic Publishers, Netherlands (2003)
17. Wouters OJ, Naci H, Samani N.J. QALYs in cost-effectiveness analysis: an overview for cardiologists. Heart. 2015 Dec 1;101(23):1868-73. doi: 10.1136/heartjnl-2015-308255. Epub 2015 Sep 22.
18. Perneger TV, Courvoisier DS. Exploration of health dimensions to be included in multi-attribute health-utility assessment. Int J Qual Health Care. 2011 Feb;23(1):52-9.
19. Department of Health. Quality of Life of Cancer Survivors in England; Report on a pilot survey using Patient Reported Outcome Measures (PROMS). December 2012. Available online at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213192/9284-TSO-2900701-PROMS.pdf (Accessed November 3, 2015)
20. Williams A. The Measurement and Valuation of Health: A Chronicle, University of York, Centre for Health Economics Discussion Paper 136. Centre for Health Economics Discussion Paper 136 1995).
21. Wu HS, Davis JE. Definition, prevalence and characteristics of sudden exhaustion: a possible syndrome of fatigue in cancer? Support Care Cancer. 2013;21(2):609–617.
22. Smith OR, van den Broek KC, Renkens M, Denollet J. Comparison of fatigue levels in patients with stroke and patients with endstage heart failure: application of the fatigue assessment scale. J Am Geriatr Soc. 2008;56(10):1915–1919.
23. Borneman, T. Assessment and Management of Cancer-Related Fatigue. Journal of Hospice & Palliative Nursing: April 2013 - Volume 15 - Issue 2 - p 77–86.
24. Hofman M, Ryan JL, Figueroa-Moseley CD, Jean-Pierre P, Morrow GR. Cancer-related fatigue: the scale of the problem. Oncologist. 2007; 12(suppl 1):4–10.
25. Ahlberg K, Ekman T, Gaston-Johansson F, Mock V. Assessment and management of cancer-related fatigue in adults. Lancet. 2003 Aug 23;362(9384):640-50.
26. Kennedy I. Appraising the value of innovation and other benefits: a short study for NICE. London, 2009.
27. Wailoo A, Davis S, Tosh J. The incorporation of health benefits in cost utility analysis using the EQ-5D. School of Health and Related Research, University of Sheffield. November 2010. Available online at: http://www.nicedsu.org.uk/PDFs of reports/DSU EQ5D final report - submitted.pdf (Accessed October 14, 2015).
28. Stone P, Richardson A, Ream E, et al. (2000) Cancer-related fatigue: Unimportant, inevitable and untreatable? Results of a multi-centre patient survey. Ann Oncol 11(8) 971–975.
29. Conner-Spady B, Cumming C, Nabholtz J-M, et al. Responsiveness of the EuroQol in BC patients undergoing high dose chemotherapy. 43. Qual Life Res. 2001;10:479-486.
30. Krabbe PFM, Stouthard MEA, Essink-Bot ML, Bonsel GJ. The effect of adding a cognitive dimension to the EuroQol multiattribute health-status classification system. J Clin Epidemiol. 1999;52(4):293–301.
31. Gudex C. Are we lacking a dimension of energy in the EuroQol instrument? Paper presented at the 8th Plenary Meeting of the EuroQol Group. Lund, Sweden: EuroQol Conference Proceedings; 1991
32. Calvert M, Blazeby J, Altman DG, Revicki DA, Moher D, Brundage MD. Reporting of patient-reported outcomes in randomized trials. The CONSORT PRO extension. J of the American Medical Association. 2013, 309(8): 814-22.

33. Ganz PA, Cotay CC. Use of patient reported outcomes in phase III cancer treatment trials: lessons learned and future decisions. J Clin. Oncol. 2007, 25(32): 5063-9.
34. European Medicines Agency. Reflection paper on the use of patient reported outcome (PRO) measures in oncology studies. EMA/CHMP/292464/2014. 17 June 2014. Available through: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500168852.pdf ; Accessed 18 January 2016.
35. Dolan P., Kind P. Inconsistency and health state valuations. Soc Sci Med. 1996 Feb;42(4):609-15.

List of figures

Figure 1. Proportion of patients across all sample and main disease areas reporting aspects not captured by the EQ-5D-5L

Figure 2. Proportion of patients across all sample and main disease areas reporting that important QoL aspects changed over the course of their illness

Figure 1

Proportion of patients across all sample and main disease areas reporting aspects not captured by the EQ-5D-5L

Note: **RD**=rare diseases; **BC**=breast cancer; **RA**=rheumatoid arthritis; **BLC**=blood cancers.

Figure 2

Proportion of patients across all sample and main disease areas reporting that important QoL aspects changed over the course of their illness.

Note: **RD**=rare diseases; **BC**=breast cancer; **RA**=rheumatoid arthritis; **BLC**=blood cancers.

Table 1. Most common aspects not captured by the EQ-5D-5L, as reported across all sample and main disease areas of the study.

	Fatigue	SEs	Co-Morbidities[1]	Relationships/ social life	Medical social care received	Cognitive impairment	Sleep deprivation	Family relationships	Fear for future	Work limitation	Financial issues
All sample (n=325)	19% (n=62)	12% (n=39)	9.5% (n=31)	6.5% (n=21)	6.2% (n=20)	4.3% (n=14)	4.3% (n=14)	3.7% (n=12)	3.7% (n=12)	3.7% (n=12)	2% (n=7)
BC (n=83)	22% (n=18)	19% (n=16)	2.4% (n=2)	4.8% (n=4)	8.4% (n=7)	8.4% (n=7)	1.2% (n=1)	2.4% (n=2)	4.8% (n=4)	1.2% (n=1)	2.4% (n=2)
BLC (n=11)	9.1% (n=1)	18.2% (n=2)	18.2% (n=2)	9.1% (n=1)	-	9.1% (n=1)	-	18.2% (n=2)	18.2% (n=2)	-	-
RA (n=14)	28.6% (n=4)	14.3% (n=2)	7.1% (n=1)	7.1% (n=1)	7.1% (n=1)	-	7.1% (n=1)	-	-	7.1% (n=1)	-
RD (n=66)	19.7% (n=13)	3% (n=2)	12.1% (n=8)	15.1% (n=10)	6% (n=4)	4.5% (n=3)	1.5% (n=1)	4.5% (n=3)	-	5% (n=3)	4.5% (n=3)
Asthma (n=11)	-	9.1% (n=1)	-	9.1% (n=1)	-	-	9.1% (n=1)	9.1% (n=1)	-	9.1% (n=1)	-

[1] Co-morbidity is defined as the presence of two or more disorders whose association is likely to occur more often than would happen by chance [32]

Table 2. Most common aspects of patients' illness that had a big impact on their health and that changed over the course of their disease

	Changes on EQ-5D-5L aspects				Changes on aspects not included in the EQ-5D-5L						
	Mobility	Usual Activities	Pain/ Discomfort	Anxiety/ Depression	Fatigue	SEs	Treatment received	Work limitation	Relationships/ Social life	Co-morbidities	Cognitive impairment
All sample (n=370)	12.4% (n=46)	4.3% (n=16)	14% (n=5)	2.7% (n=10)	17% (n=63)	11.4% (n=42)	7% (n=26)	6.5% (n=24)	3.8% (n=14)	3% (n=11)	2.7% (n=10)
BC (n=86)	3.5% (n=3)	7% (n=6)	24.4% (n=21)	12.8% (n=11)	18.6% (n=16)	23.2% (n=20)	4.6% (n=4)	5.8% (n=5)	1.2% (n=1)	2.3% (n=2)	1.2% (n=1)
BLC (n=13)	23% (n=3)	-	15.4% (n=2)	15.4% (n=2)	23% (n=3)	7.7% (n=1)	7.7% (n=1)	15.4% (n=2)	7.7% (n=1)	15.4% (n=2)	7.7% (n=1)
RA (n=19)	21% (n=4)	-	5.2% (n=1)	10.5% (n=2)	10.5% (n=2)	-	-	5.2% (n=1)	5.2% (n=1)	5.2% (n=1)	-
RD (n=79)	18.9% (n=15)	3.8% (n=3)	10.1% (n=8)	-	10.1% (n=8)	2.5% (n=2)	6.3% (n=5)	8.8% (n=7)	6.3% (n=5)	8.8% (n=7)	3.8% (n=3)
Asthma (n=15)	13.3% (n=2)	6.6% (n=1)	-	13.3% (n=2)	13.3% (n=2)	20% (n=3)	-	6.6% (n=1)	-	6.6% (n=1)	-

Source: The authors.

Appendix

Table1. All disease diagnoses reported by participants

Cancer	**(n=329)**
Breast	180
Myelodysplastic Syndrome (MDS)	55
Blood	31
Kidney	15
Melanoma	9
Cancer	9
Brain tumor	2
Medula Blastoma	2
Glioblastoma Multiforme (GBM)	2
Astrocytoma	1
CRC	5
Ovarian	4
Oesophageal	3
Prostate	3
Thyroid	2
Lung	2
Appendix	2
Angiosarcoma	1
Duodenal	1
Multiple cylindromas	1
Arthritis	**(n=100)**
Rheumatoid Arthritis	53
Ankylosing Spondylitis	18
Psoriatic A	14
Arthritis	5
Osteoarthritis	1
Inflammatory	1
Palindromic rheumatism	1

Rare diseases	**(n=140)**
A1-Antitrypsin deficiency	6
Acute Intermittent Porphyria	1
Adamantiades- Behcet syndrome	1
Addison's disease	1
Adrenomyeloneuropathy	3
Alport Syndrome	1
Ataxia (ADCA,SCA)	21
Chronic granulomatous disease (CGD)	3
Chronic infantile neurological cutaneous and articular (CINCA) syndrome	1
Churg-Strauss Syndrome	1
Common Variable Immune Deficiency (CVID)	2
Complex regional pain syndrome	1
Cryoglobulinemia	1
Cystic Fibrosis	1
Dercum's Disease (Adiposis Dolorosa)	1
Duchenne Muscular Dystrophy (DMD)	6
Ehlers Danlos Syndrome (EDS)	40
Erythromelalgia	1
Familial Lipoprotein Lipase Deficiency	1
Fibroydisplasia Ossoficans Progresiva	1
Fragile X syndrome	1
Gaucher disease	1
Guillain–Barré syndrome (GBS)	3
Hemophilia	1
Hyper IgE Syndrome (Primary Immune Deficiency)	1
Hypocomplementemic urticarial vasculitis syndrome (HUVS)	1
Idiopathic Intracranial Hypertension	1
Juvenile Idiopathic Arthritis	8
Klippel-trenaunay syndrome	1
Mal de Debarquement Syndrome	1
Mitchondrial Neurogastroinestinal Encephalomyopathy (MNGIE)	1
Mixed Connective Tissue Disease	1
Myotonic Dystrophy	1
Neuromyelitis Optica (NMO)	1
Painful Bladder Syndrome	2
Paroxysmal Nocturnal Haemaglobinuria	1
Prader Willi Syndrome (PWS)	1
Primary Antibody Deficiency	1
Primary sclerosing cholangitis (PSC)	1
Pudendal Neuralgia	1
Pure Autonomic Failure	1
Retinitis Pigmentosa (RP)	1
SAPHO syndrome	1
Stargardt disease	1
Still syndrome	1
Systemic sleroderma	5
Tuberous sclerosis	2
Wegener's Granulomatosis/Granulomatosis with polyangiitis (WG/GPA)	3
X-linked agammaglobulinemia (XLA)	1

Other diseases	**(n=198)**
Asthma	24
Essential Tremor	23
Systemic Lupus Erythematosus (SLE)	18
Restless Leg Syndrome (RLS)	17
Hypermobility Syndrome (HMS)	16
Psoriasis	13
HIV	9
Multiple Sclerosis	8
Gastroparesis (GP)	7
Diabetes	6
Stroke	6
Parkinson's disease	5
Hypertension	4
Adrenal Deficiency Hyperactivity Disorder (ADHD)	3
Chronic Obstructive Pulmonary Disorder (COPD)	3
Fybromyalgia	3
Sjogren's syndrome	4
Crohn's disease	1
Mediainfract ACI-occlusion	2
Migraine	2
Raynaud's syndrome	2
Allergic Rhinitis	1
Allergy	1
Antiphospholipid syndrome	1
Apoplexy	1
Autosomal dominant polycystic kidney disease (ADPKD)	1
Borderline Personality Disorder	1
Chronic Cystitis	1
Chronic Fatigue Syndrome	1
Cluster headaches	1
Coeliac disease	1
Depression	1
Diffuse idiopathic skeletal hyperostosis (DISH)= Forestiers disease	2
Dysautonomia	1
Encephalomyelitis	1
Genetic disease	1
Haemorrhagic Ulcerative Collitis (RCUH)	1
Hashimoto thyroiditis	1
Kidney failure	1
Lower back pain	1
Lymphoedema	1
Macular degeneration	1
Myelofibrosis	1
Oesteoprosis	1
Persistent pelvic pain	1
Pulmonary hypertension	1
Sleep apnoea	1
Thrombosis	1

Table 2

Sample demographic and HRQoL characteristics

	All sample (n=767)	BC (n=180)	RD (n=140)	RA (n=53)	BLC (n=31)	Asthma (n=24)
Employment and demographics						
Age, mean (SD)	50 (14.13)	53 (9.3)	41 (14.4)	47 (11.2)	57 (12.6)	49 (17)
Age at diagnosis, mean (SD)	39 (17.5)	48 (9.8)	29 (17.3)	29 (14.4)	48 (13)	17 (16)
Gender; Female, n (%)	592 (77%)	179 (99%)	111(79%)	46 (86%)	16 (51%)	19 (79%)
Marital status, n (%) **Single** **Married or cohabiting** **Divorced** **Separated** **Widow**	 174 (22%) 513(67%) 50(6.5%) 15(1.9%) 15 (1.9%)	 21(11%) 138 (76%) 12 (6.6%) 8 (4.4%) 1 (0.5%)	 57 (40%) 77 (55%) 4 (2.8%) 1(0.7%) 1(0.7%)	 12 (22%) 32 (60%) 6 (11%) 1 (1.9%) 2 (3.8%)	 6 (19%) 21(67%) 2 (6.5%) 0 2 (6.5%)	 11 (46%) 11 (46%) 1 (4%) 1 (4%) 0
Employment status, n (%) **Employed** **Unemployed** **Temporary sick leave** **Permanent work disability** **Retired** **Housewife/husband** **Student** **Other (i.e. self-employed)**	 312(40.7%) 27 (3.5%) 58(7.5%) 19 (2.5%) 83 (10.8%) 182(23.7%) 30 (3.9%) 56 (7.3%)	 93 (51%) 1 (0.5%) 7 (3.9%) 9 (5%) 16 (8.9%) 30 (16.6%) 9 (5%) 15 (8.3%)	 50 (3.5%) 14 (10%) 18 (12.8%) 2 (1.4%) 33 (2.3%) 8 (5.7%) 7 (5%) 8 (5.7%)	 24 (45%) 1 (1.9%) 5 (9.4%) 1 (1.9%) 3 (5.6%) 8 (15%) 6 (11.3%) 5 (9.4%)	 12 (38.7%) 0 1 (3.2%) 2 (6.5%) 0 14 (45%) 0 2 (6.5%)	 10 (41%) 1(4%) 1(4%) 0 4 (16%) 7 (29%) 0 1 (4%)
HRQoL characteristics						
EQ-5D-5L Utility, mean (SD)	0.62(0.27)	0.7 (0.18)	0.46 (0.31)	0.58 (0.2)	0.73 (0.16)	0.74 (0.24)
Utility loss, mean (SD)	0.24 (0.27)	0.15 (0.18)	0.4 (0.31)	0.27 (0.2)	0.12 (0.16)	0.12 (0.24)

Note: **RD**=rare diseases; **BC**=breast cancer; **RA**=rheumatoid arthritis; **BLC**=blood cancers.

Table 3. Text responses indicating that, according to patients, daily variations of their wellbeing, as well as specific aspects of the existing EQ-5D-5L domains were not captured by the tool

Disease	Mobility	Pain/Discomfort	Anxiety/Depression	Daily variations
BC		• *"Unexplained back/uterus pain"* • *"Joint pain"* • *"Control of chronic joint pain"*	• *"Anxiety for relapse"* • *"Stress at minimal follow up care"* • *"Anxiety although better now"* • *"Certain situations make me more anxious about it – e.g. travelling to remote places in case I get cellulitis and septicaemia again"* • *"Long term anxiety over lack of full checkups"* • *"Well-being/stress"*	• *"It could go into **more detail**. I am single with no children and not living with family. My quality of life is partly about whether I can go out and do the usual things I enjoy doing - e.g. go walking, to the cinema etc and also whether I am well enough to earn my living as I have nobody else to support me".* • *"It **barely scratches the surface**"*
RD	• *"Losing mobility"* (Male, Fibrodysplasia Ossoficans Progressiva patient) • *"Loss of ambulation; ventilation" (Male, DMD patient)*	• *"Headaches/Specific pain" (Male, EDS patient)* • "Pain dislocations fractures" (Female, EDS patient) • *"The pain" (Male, ADCA[2] patient)*	*"Psychological toll; feeling quite separated from the mainstream of life in order to manage years of depression when wasn't able to cope." (Female, Familial Lipoprotein Lipase Deficiency patient)*	• *"**Too general** - I can dress up by myself, but sometimes I have problems with pants' buttons"* (Female, JIA patient) • *"My **health can change rapidly** even by the minute. I can have a good and a bad day"* (Female EDS patient). • "Something that **captures acute as well as chronic**, something that acknowledges flare ups" (Female EDS patient)
Asthma		*"Breathlessness was not included and it is unclear whether this is included in the pain/discomfort section"*		*"Asthma is not a stable disease, so it **is hard to give a general indication"***
Other	• *"Was not able to walk"* (Female, Stroke patient) • "Cannot run" (Female, RA patient) • "*Paralysed*" (Male, KC[3] patient) • "*Couldn't walk properly for 4 months after chemo finished*". (Male, CRC[4] patient)	• *"Neuropathic pain"* (Male, Diabetes patient) • *"The impact of pain on all aspects of my life including social*" (Female, Persistent Pelvic pain patient) • *"Fibromyalgia" (Female, RA patient)* • *"Aches pain muscle ache burning in back burning in shoulder" (Male, KC patient)* • *"Muscle pain" (Female, KC patient)*	• "I am not receiving help for the anxiety caused by my illness" (Female, RLS patient) • *"I only get about 4 hours sleep per night but have to carry on as normal. It leads to depression as I have not slept properly in years"* (Male, RLS patient) • *"Emotional health (which I don't think 'anxiety or depression' captures - its more about feeling happy, having good well-being, etc." (Female, Oesophageal cancer patient)* • *"Anxiety/depression is too specific. Living with terminal cancer has far more subtle effects than depression/anxiety". (Male, Oesophageal cancer patient)*	• *"It **only measures one day** whereas many conditions result in varying abilities across different days". (Male MDS patient)* • *"Each day is different so taking it for just one day is not indicative of the overall effects" (Female, Gastroparesis patient)* • *"**Variability** day to day, week to week, month to month" (Male, Lower Back Pain patient)*

[2] ADCA=Autosomal Dominant Spinocerebellar Ataxia
[3] KC=Kidney cancer
[4] CRC=Colorectal cancer