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Review

Quality-adjusted time without symptoms or toxicity (Q-TWiST): patient-reported outcome or mathematical model? A systematic review in cancer

Wendy R. Tate[1,2]* and Grant H. Skrepnek[3,4]
[1]*College of Pharmacy, The University of Arizona, Tucson, AZ, USA*
[2]*The University of Arizona Cancer Center, The University of Arizona, Tucson, AZ, USA*
[3]*College of Pharmacy, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA*
[4]*Peggy and Charles Stephenson Cancer Center, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA*

**Correspondence to:*
The University of Arizona Cancer Center, The University of Arizona, 1515 N. Campbell Ave. Room 1922, PO Box 245024, Tucson, AZ 85724-5024, USA.
E-mail: wrtate@email.arizona.edu

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Abstract

***Objective*: Successful cancer treatment is defined as an increase in overall survival and/or progression-free survival. Despite their importance, these metrics omit patient quality of life. Quality-adjusted time without symptoms or toxicity (Q-TWiST) was developed to adjust survival gained, accounting for quality of life. The purpose of this systematic review was to assess the methods reported in cancer literature to determine Q-TWiST values and how these are currently translated to the clinic.**

***Methods*: The Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were used to conduct a systematic review of studies indexed on MEDLINE and Web of Science through April 2013. Cancer studies that measured Q-TWiST either as a primary outcome or retrospectively and determined utility coefficients from a patient population were identified, and their methods reviewed to determine how the utility coefficient was calculated. Additionally, other relevant factors such as definitions of health states and significant findings were collected and summarized.**

***Results*: Out of 284 studies, 11 were identified that calculated patient-defined utility coefficients. Several methods to determine utility coefficients were reported, and multiple definitions of health state toxicity were applied. Of these studies, seven reported significant differences ($p < 0.05$) in quality-adjusted survival. No studies, however, directly discussed the clinical relevance of their findings.**

***Conclusions*: Currently, Q-TWiST is utilized as a mathematical theory rather than a clinical tool. Standardization of terminology plus reliability and validity testing of determining both utility coefficients and time frame definitions must be performed before Q-TWiST can become clinically useful to physicians and patients alike for making treatment decisions.**

Introduction

The endpoint of many cancer clinical trials is overall survival (OS) time, progression-free survival (PFS), or relapse (REL). Despite their given importance, however, these measures do not formally account for the quality of life (QoL) that a person has from survival gains and whether it is of better quality than other treatments. A method to capture the QoL sustained (or lost) owing to a specific treatment regimen was developed by Goldhirsch *et al.* and is called quality-adjusted time without symptoms or toxicity (Q-TWiST) [1].

The Q-TWiST is based on time without symptoms or toxicity (TWiST), which was developed in 1987 as survival analysis tool for cancer [2]. Q-TWiST quantifies data from patient-reported outcome (PRO) tools into survival calculations. By using a utility coefficient (i.e., the weight that the given stage has) and the amount of time spent in the different health states of disease, OS is adjusted to reflect the quality of that time. Utility, derived from the economic literature, is a broad concept that embodies preferences for a given state of being often relating to a good (a physical product, such as prescription medications or chemotherapy) or service (an action or work carried out for someone, such as clinical consultation).

The Q-TWiST involves three states: (1) toxicity (TOX); (2) TWiST; and (3) REL (or disease progression). The time spent in each of these states is multiplied by the utility coefficient for that state as follows:

$$\text{Q-TWiST} = \text{uTOX}*\text{TOX} + \text{uTWiST}*\text{TWiST} + \text{uREL}*\text{REL} \quad (1)$$

Utility coefficients range on a scale from 0 (*worst stage imaginable or death*) to 1 (*perfect health*). The utility coefficient can be measured directly (e.g., using the standard gamble method), indirectly using QoL questionnaires (e.g., the EQ-5D) to determine proxy utility

coefficients, or they can be arbitrarily set. For example, if TWiST is equal to the most desirable value (i.e., utility coefficient of 1, which is equal to perfect health) and a day of chemotherapy TOX is only worth half of that (i.e., the quality of 2 days of experiencing toxicity is equal to having 1 day of perfect health), then the utility coefficient of TOX is 0.5. The interpretation of this measure is specific for the condition or disease, the treatment(s) studied, the utility coefficients applied, and the time frame that was studied [3].

The Q-TWiST calculations can be conducted prospectively using PROs as part of a clinical trial to measure utility coefficients or retrospectively calculated using previously obtained data or arbitrarily set coefficients [3]. In order to generalize the Q-TWiST information, sensitivity or threshold analyses can be conducted [4]. These analyses, which set the TWiST state to 1, project the entire range of Q-TWiST outcomes for differing combinations of utilities of TOX and REL.

Since the original description of Q-TWiST in 1989, the variability of cancer treatment regimens has led to an expansion of the Q-TWiST model. The traditional model of three health states has been expanded to include successive treatments, allowing each separate treatment protocol to be accounted for individually [5–7]. Murray *et al.* calculated the variance and sample size equations for Q-TWiST analyses to design appropriately powered trials [8]. Taking Q-TWiST one step farther, Cole *et al.* incorporated regression variables into the Q-TWiST analysis, creating a Q-TWiST–Cox regression hybrid analysis and accounting for other variables of survival [9]. In addition to expanding analyses, several types of Q-TWiST plots have been developed to graphically portray the findings of specific Q-TWiST calculations as well as the broader threshold analyses [10]. Finally, Q-TWiST has been adapted and applied to other conditions, such as AIDS, multiple sclerosis, and vascular disease [11–13]. Given the numerous issues presented with its use in oncology research, the purpose of this review was to assess the methods reported in the cancer literature to determine Q-TWiST values and how they are currently translated to the clinic.

Materials and methods

Review protocol

This study was conducted utilizing the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [14]. No formal review protocol exists beyond this paper. The protocol for this study has not been registered with any registry website that documents methods of reproducing systematic reviews.

The Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool was used to assess this review [15]. The AMSTAR guidelines, published by Shea *et al.*, describe 11 criteria that assess the methodological quality of systematic reviews. Applicable criteria outlined by the AMSTAR guidelines were met, as described in greater detail later.

Human subjects

This project did not include human subjects, as none of this information is private, is individually identifiable, or was obtained through intervention or interaction with human beings. Institutional review board approval was not necessary.

Inclusion/exclusion criteria

Studies were included if the target disease was cancer and Q-TWiST was quantitatively assessed. A subset of studies was further reviewed if the utility coefficients were determined from the subject population or another patient population relevant to the study sample. Studies were excluded if they did not directly measure QoL using the Q-TWiST method (e.g., quality-adjusted life years (QALY)) or measured a disease state other than cancer. Conference proceedings were not included as either they did not thoroughly describe the determination of the utility coefficients or the study was published fully elsewhere. Meta-analyses were included if an author presented new Q-TWiST calculations.

Search strategy

PubMed, Web of Knowledge, and the Cochrane Library were all searched using the term 'Q-TWiST'. All databases limited the search to English papers and searched all literature up through 30 April 2013. PubMed utilized the following additional limits: human and cancer. Web of Knowledge searched for Q-TWiST separately under topic and terms. The Cochrane Library searched for Q-TWiST under title, abstract, or keywords and searched all available databases. Additional articles were included if referenced in an included study but not identified through the database search.

English-only papers were abstracted as the primary reviewer (W. T.) only speaks English. The databases chosen were based on institutional availability. No additional contact with authors of the downloaded papers was made. Reference management was carried out through RefWorks 2.0 (RefWorks COS, Bethesda, MD).

Review of studies

Studies were screened and reviewed independently by the primary author (W. T.). Initial parameters of interest were determined prior to screening studies in order to reduce the risk of bias. These included demographics of the studies (e.g., number of subjects, clinical trial protocol,

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and site and stage of cancer); whether the utility coefficients were measured directly or indirectly or arbitrarily constructed; treatments studied; whether the study found a difference by utilizing the Q-TWiST method; and whether that finding was statistically significant and/or clinically relevant. Upon study of the selected papers, additional information regarding the methods used to quantitate the utility coefficient and formula to calculate Q-TWiST was abstracted and analyzed. Unless otherwise described in the source paper, it was assumed that only one measure was taken to estimate the utility coefficient for any given health state. Abstracted study data were reviewed by a second reviewer (G. S.) to determine if any additional data items should be obtained.

This study qualitatively assessed the prevalence of assessing Q-TWiST as part of cancer treatment. Although the actual finding of whether the treatments studied had a difference in quality-adjusted survival was reviewed, it was not the primary endpoint of this review.

Results

Studies

Two-hundred and eighty-four papers (69 from PubMed, 117 from the topic search of Web of Knowledge, 52 from the title search of Web of Knowledge, and 46 from the Cochrane Library) were initially identified through the database analysis described in the Materials and Methods section. Three additional papers were identified through reference checks. After duplicates were removed (the same reference being identified through multiple search engines), 137 studies remained. Of these 137 studies, 126 studies were discarded as described in Figure 1, leaving 11 studies that reported patient-derived utility coefficients. Of the remaining 11 studies, five were breast cancer trials, and one study was published in each of the following cancer sites: colon/rectal, melanoma, lymphoma, lung, renal, and prostate (Table 1). All Q-TWiST analyses were performed as either secondary objectives or retrospective analyses of randomized controlled trials. Trials ranged from 95 to 1400 subjects. Seven studies (63.6%) reported a significant difference in at least one measure of quality-adjusted time. No study performed a power analysis of the Q-TWiST objective.

Calculation of utility coefficients

The method for calculating the utility coefficients varied between studies. Most studies utilized a health index, whereas other studies had a battery of health questionnaires. The EQ-5D and the subjective health estimation were used to calculate utilities in two studies (18.2%) each [19,20,26,22]. Three (27.3%) studies used utility weights from non-study participants with similar cancers [24,23,17]. Two studies (18.2%) used utility scores estimated by oncology professionals [16,18].

Two (18.2%) studies explicitly stated that they used the median or average score of multiple assessments to calculate the utility coefficient [25,19]. One other study only performed sensitivity analyses on several values of health states [21].

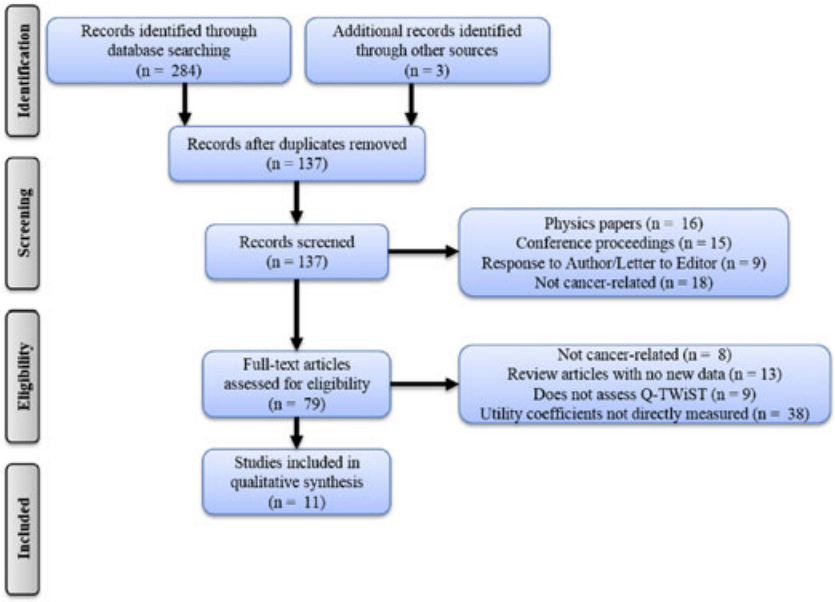

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flowchart documenting the number of studies meeting inclusion criteria and reasons for exclusion from the review on the basis of the study's search strategy [14]

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Table 1. Description of studies that measured Q-TWiST utility coefficients directly or utilized a previously determined coefficient in a similar population ($n = 11$)

Primary author (citation)	Year published	Cancer	Number of subjects	Study protocol number	Treatments studied	Finding
Fairclough [16]	1999	Breast; hormone receptor negative, node positive	163	EST-3189	Six cycles of cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) or a 16-week regimen	16-week treatment experienced increased Q-TWiST over the 6-cycle treatment ($p < 0.05$)
Kilbridge [17]	2002	Melanoma; high-risk, resected, cutaneous	95	E1684 and E1690/ S9111/C9190	Adjuvant IFNα2b chemotherapy versus observation	77% had slightly increased quality-adjusted survival (NS)
Nooij [18]	2003	Breast; post-menopausal, non-progressing, metastatic	204	None	Post-induction chemotherapy versus no treatment	Treatment increased quality-adjusted survival to 8.4 months from 7.9 months (NS)
Bernhard [19]	2004	Breast; post-menopausal	1398	Breast Cancer Study Group Trial IX	Tamoxifen versus CMF followed by tamoxifen	Combo improved the health state and overall survival for ER-negative women ($p = 0.03$); no benefit for ER-positive women
Bernhard [20]	2008	Breast; 6 weeks post-surgery	344	IBCSG Trial 15-95	Standard dose chemotherapy (AC or ECx4 followed by CMFx3) or DI ECx3	DI epirubicin and cyclophosphamide administered with filgrastim and progenitor cell support (DI-EC) had a slight gain in quality of life (NS)
Sherrill [21]	2008	Breast; advanced or metastatic HER2+, progressive disease after previous treatment	399	None	L + C versus capecitabine	L + C combination had an increase in Q-TWiST of at least 4 months for all utilities for relapse under 0.9; increase in Q-TWiST of 6.1 weeks with the observed coefficients ($p < 0.05$)
Zbrovek [22]	2010	Renal; stage IV or recurrent	626	Global ARCC	Temsirolimus versus IFNα versus combination	Mean survival of temsirolimus was 1.9 months longer than IFNα or combo group ($p = 0.0005$); 1.8 months in the TWiST state ($p = 0.0015$)
Marcus [23]	2010	Non-Hodgkin's lymphoma; advanced follicular	321	M39021	R-CVP versus CVP alone	R-CVP gained a mean of 15.17 months; 11.30 months less time in relapse, no increase in toxicity; 8.33 months longer Q-TWiST compared with CVP ($p < 0.001$)
Rosendahl [24]	1999	Prostate; T, N, and G categories categorized as M1, no previous systemic treatment	297	EORTC Trial 30853	Orchiectomy versus Zoladex and flutamide	Drug combo increased Q-TWiST 5.3 months (NS)
Jang [25]	2009	Non-small cell lung	359	JBR.10	Adjuvant vinorelbine and cisplatin versus observation	Adjuvant therapy increased Q-TWiST by 5–6 months, on average ($p < 0.05$)
Wang [26]	2011	Colon, rectal; metastatic with wt-KRAS	243	None	BSC versus panitumumab + BSC; cross-over study design	Combo increased quality-adjusted progression-free survival to 12.3 weeks from 5.8 weeks; 73–104% increase in median progression-free survival ($p < 0.0001$)

Demographics, including author, year published, cancer site/state, number of subjects in the study, protocol number, treatments studied, and a brief discussion of the study's findings for the 11 studies that met all of the inclusion criteria for the study ($n = 11$) are summarized.
Q-TWiST, quality-adjusted time without symptoms or toxicity; NS, not statistically significant; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; ER, estrogen receptor; DI, dose intensive; BSC, best supportive care; L + C, lapatinib + capecitabine; CVP, cyclophosphamide, vincristine, and prednisone; R-CVP, CVP + rituximab.

One study [25] estimated utility coefficients using three different methods and then compared each of those methods with arbitrarily assigned utility coefficients. Regardless of the method used, a statistically significant gain in quality-adjusted time (approximately 5–6 months in non-small cell lung cancer) was seen with the addition of adjuvant therapy.

Toxicity

Upon review, it was found that the definition of TOX differed between studies, each definition calculating the utility coefficient differently. Two broad definitions were identified in the present analysis. The first definition was based on treatment duration. As long as the subject was

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undergoing treatment for cancer, they were considered in the TOX stage, regardless of whether adverse events were experienced. Three (25%) studies used this definition of TOX [16,18,19]. The second definition of TOX in the literature was based on adverse events. This category could be further defined via two sub-categories: (1) the number of days that a subject experienced an adverse event and (2) the assignment of a fixed period for the experience of an adverse event. In the first sub-category, the time a subject experienced an adverse event was accounted according to day. In the second, the report of a specific adverse event would be assigned a period that accounts for not only the TOX that a subject experiences but also the recovery time associated with the event. From the limited methods provided in the eight studies that utilized this second definition, four (50%) measured days of adverse events, whereas the other four (50%) assigned a more standard time value to categories of adverse events. Adverse events that were considered to affect QoL were defined on a protocol-by-protocol basis. Most studies set a threshold of a grade III or grade IV event that was not a laboratory event, which means that the subject could feel the effect of the event, theoretically impacting their QoL [20,21,26,22]. One study set grade II as the threshold [25]. The prostate study picked the most common life-altering adverse event and calculated TOX on that event alone [24].

Time without symptoms or toxicity

In the mathematical model of Q-TWiST, the TWiST state is set equal to 1 (perfect health). When derived from patient questionnaires, this value was found to be less than 1 in every study (Table 2). Likewise, the range of values that were obtained for both the TOX and REL states varied in range between studies.

Relapse

Most studies utilized right censoring if an event (regression or death) was not experienced by the end of the study [19–21,26,22,23]. For studies that had varying follow-up times, the restricted means method was often utilized. This method uses the median follow-up time as the length of overall follow-up. Four (36.4%) studies used the restricted means method in their Q-TWiST analysis [25,16,18,24].

Arbitrarily assigned utility coefficients

In addition to the 11 studies that calculated utility coefficients, 38 studies analyzed Q-TWiST by assigning arbitrary utility coefficients, utilizing a sensitivity analysis, and/or performing a threshold analysis for both TOX and REL [1,2,5–9,27–57]. Seven studies used clinical trial data to provide an example of the mathematical models of Q-TWiST and did not specifically assess the treatment protocol [8,9,27–31]. In these 38 studies, TWiST was always assumed to be 1 (perfect health). Commonly used TOX and REL utility coefficients included 0.25, 0.5, 0.75, 0.8, and 1. Most studies found that there was a threshold of utility coefficient pairings that favored one treatment over another [6,32,33]. A few studies showed a preference of one treatment over another treatment at all utility pairings [34]. Some studies paired this information with information about QALY [35–40].

Meta-analyses

Three meta-analyses met the inclusion criteria for this study. Cole *et al.* reported a meta-analysis of eight trials where no patient-level data were available and attempted to assess the trade-offs of adjuvant chemotherapy in breast cancer [58]. The authors concluded that individual patient data were not required if the results of the overall Q-TWiST analysis were available. This was carried out by assuming the mean duration of time in TOX on the basis of previous

Table 2. Utility coefficients for toxicity, relapse, and TWiST states

Cancer (study author, year, citation)	Method of determination	TOX	REL	TWiST
Breast (Fairclough, 1999, [16])		0.9 (CAF), 0.8 (16 weeks)	0.6	
		0.8 (CAF), 0.7 (16 weeks)	0.5	
Breast (Nooij, 2003, [18])		0.54	0.29	0.73
Breast (Bernhard, 2004, [19])		0.89	0.71	0.91
Breast (Bernhard, 2008, [20])		0.77	0.77	0.91
Breast (Sherrill, 2008, [21])	Patient questionnaires	0.9	0.65	Normalized to 1
Colorectal (Wang, 2011, [26])	Patient questionnaires	0.6008	0.6318	0.7678
Renal (Zbrozek, 2010, [22])		0.585	0.587	0.689
Lung (Jang, 2009, [25])	Patient questionnaires	0.57–0.86	0.50–0.83	0.75–1.0
Lymphoma (Marcus, 2010, [23])		0.618 (assumed)	0.618	1.0 (assumed)
Melanoma (Kilbridge, 2002, [17])		No means provided		
Prostate (Rosendahl, 1999, [24])		0.98	0.93/0.88	N/A

The utility coefficients and how they were measured from the 11 studies that derived patient coefficients for each health state: toxicity (TOX), relapse (REL), and time without symptoms or toxicity (TWiST) were extracted from each paper and tabulated.

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studies, as well as assign arbitrary utility coefficients ($u_{TOX} = u_{REL} = 0.5$) and the utility coefficient for the TWiST state as 1. In addition to performing a bootstrap analysis to strengthen the statistical assessment, a threshold analysis was performed to cover all possible utility combinations.

Also, in 1995, the same group reported a meta-analysis of the same eight trials as mentioned earlier but using some patient-level data for defining time frames for each health state [59]. Similar to the Cole *et al.* [58] meta-analysis, utility coefficients were assigned arbitrarily, and a threshold analysis was performed by Gelber *et al.* [59]. Very similar results regarding the quality-adjusted survival for treatment were found.

Gelber *et al.* also conducted a meta-analysis for adjuvant tamoxifen in early breast cancer [60] Again, similar to Cole *et al.* [58] meta-analysis, Q-TWiST values from each of the nine studies were used in the meta-analysis, but no patient-level data were obtained. All three meta-analyses yielded threshold analyses and hypothetical survival curves for quality-adjusted survival in breast cancer, but no conclusions were presented regarding clinical relevance.

Discussion

Of the 284 total initial articles, this systematic review found 11 studies that specifically measured the utility coefficients for Q-TWiST health states in cancer since its debut in 1989. An additional 38 studies and three meta-analyses were identified that used a threshold analysis and/or used arbitrary utility coefficients. Many of these studies were retrospective analyses of previous trial data where the original trial never intended to collect data to specifically measure Q-TWiST. The majority of studies that applied the Q-TWiST method were in breast cancer, which was the original condition to which the Q-TWiST model was applied. Although almost two-thirds of the studies found a statistical difference in quality-adjusted survival, no studies described whether the difference seen was clinically significant or followed up with subjects to validate the quality or value of the gain in time experienced.

This study improves on the current research in that it updates the work of Revicki *et al.* to specifically examine patient-derived utility coefficients and the methodology regarding how they are collected [61]. It also articulates the inconsistencies in this method of assessing patient-reported utilities, in that utility (or its proxy) can be measured through a direct approach (i.e., standard gamble) or estimated via patient health indices (such as the SF-36 or EQ-5D), via a proxy measurement (such as physician assessment), or arbitrarily through sensitivity analyses making use of a range of utility values. Revicki *et al.* highlighted that many studies do not prospectively collect QoL data [61]. The current work suggests that this paradigm has not changed.

Although a valuable tool for physicians, the current application of Q-TWiST often appears as a mathematical model rather than a clinical tool that can be applied directly in patient care. That is, seven studies used clinical trial data purely to illustrate their mathematical model, and 38 of the 49 total studies assigned arbitrary coefficient values. Studies are difficult, if not impossible, to compare directly given that different timelines, utility coefficients, and TOX definitions are utilized. Even among the same research group, methods for determining a patient-derived utility coefficient varied between studies. The definition of TWiST is not universal, and although the definition may not change the statistical significance of one treatment regimen over another, it can completely change the interpretation. 'Perfect health' may not be the same as 'the best health expected for this disease' to a cancer patient, highlighting the fact that the source of the utility coefficient can bias the measure. In one study reviewed here, the physicians determined the utility coefficient. Work published by Einstein *et al.* found that, in ovarian cancer, the provider's utility coefficient was higher than the patient's utility coefficient [62]. Although statistical significance is determined and discussed, clinical significance is conspicuously absent from most studies. Only one original paper addressed the range of Q-TWiST values that would constitute a clinically important difference [61]. In this review, beyond Revicki's work, only two studies that discussed the calculation of Q-TWiST with utility values derived directly from the patient were found [21,61,23]. Another publication [41] also mentioned the lack of discussion regarding clinically important differences. Additional research is needed to solidify definitions, determine the best method to reliably calculate direct utility coefficients from patients, determine what amount of increased QoL is clinically relevant, and validate all of these methods. Creating standards for definitions, utility measurement and clinically relevant differences will also strengthen Q-TWiST's validity as a PRO that can be used in FDA-approved labeling information.

Even with these shortcomings, Q-TWiST improves upon the current benchmarks of OS and PFS by adding QoL. Q-TWiST is a useful tool when comparing treatments that are unclear on which is more beneficial, such as when treatments have very different TOX profiles, when comparing two very different treatments (e.g., drug versus surgery), and when comparing treatment with a longer survival time but significant TOX versus no treatment. The concept of including QoL can provide patients and their caregivers with additional information critical to making treatment decisions. Persons with cancer would benefit from having available to them information about not only how much time they may gain from a specific treatment but also of what quality that time has. Patients may find value in the ability to weigh both the expected time spent in a specific health state and the quality of that

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state. The added value of Q-TWiST is that it allows a person to see what length of time they may expect to be in a state, such as TOX, and the utility of that health state versus just seeing the total gain in life years. This can be compared with another treatment, which may have a different length of time in TOX and a different utility value for the state. This information is beneficial to physicians when deciding what course of treatment, if any, would be in their patient's best interest. Q-TWiST analyses should be considered when writing and executing a clinical trial to further the body of evidence of the effectiveness of well-rounded treatment that includes the social and emotional parts of health, as well as the physical.

There were some notable limitations in the current review. Only one reviewer performed the initial screening of studies. This limitation may have impacted the interpretation of results by introducing bias in the selection of studies (there was no 'double-check' to ensure that all appropriate studies were included for review). Studies had to be written in English in order to be included, potentially limiting the total number of studies available to be reviewed. In addition, the authors did not have access to Embase, which introduced the potential to miss some articles, particularly those of solely European origin.

Future research

This systematic review highlights the need for empirical research to be conducted to determine the mean utility coefficients for both different types of cancer and different health states (TOX, REL, and time without treatment or symptoms). A small surge of work in this area occurred in 2012; however, these studies were limited in that they focused on a specific stage of cancer and the utility determined by non-cancer patients [34,62,52]. In addition to obtaining utility coefficient values, a systematic manner of applying these coefficients to standardized, defined health states must be developed to ensure that differences seen between studies can be compared.

Conclusion

The Q-TWiST applies patient utility coefficients for three health states (TOX, time without treatment or symptoms, and REL) to the length of time a patient is in the corresponding health state. The addition of the utility coefficient adjusts the time associated with a given treatment to account for the patient's QoL. In the present study, a systematic review of the literature, 11 studies that utilized utility values from health questionnaires, patient evaluation, or oncologist expertise were identified. This review found that the definitions and utility coefficients varied between studies. Because of the inconsistencies between studies, Q-TWiST is currently utilized as a mathematical theory rather than a clinical tool. Several things must be carried out before Q-TWiST can become clinically useful to physicians and patients alike, including the standardization of terminology, reliability and validity testing, determining both utility coefficients and time frame definitions, and finally, patient and physician feedback on its usefulness in treatment decisions.

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