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Article:

Measurement of Utilities Associated with Parenteral Support Requirement in Patients with Short Bowel Syndrome and Intestinal Failure

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ABSTRACT

Purpose: Short bowel syndrome (SBS) is the main cause of intestinal failure. Intravenous supplementation (parenteral support [PS]) helps patients regain health but can affect patients' health-related quality of life (HRQoL). The value of health states associated with the number of days on PS per week is unknown in the United Kingdom. The objectives of the present study were to develop health state vignettes for SBS and PS, and to estimate health state utilities by using the time trade-off (TTO) technique.

Methods: Vignettes were developed and reviewed through various processes. Eight states described the impact of 0 days (weaned off PS) through to 7 days on PS; each state comprised the conditions, symptoms, treatments, and impacts related to EuroQol-5 dimensions. A sample of the UK general public viewed each state in interviews; they provided ratings using a visual analog scale and utility scores using the TTO. Participants completed background questionnaires.

Findings: One hundred participants rated and valued each health state. Visual analog scale and utility scores showed a steady decline for the health states associated with increasing numbers of days on PS. With "full health" equivalent to a utility score of 1, the most burdensome state was "7 days on PS" (mean [SD]

utility score, 0.36 [0.35]), whereas weaned off ("0 days on PS") showed the least burden (0.82 [0.22]).

Implications: More days of PS are perceived by members of the public to have an increasing negative impact on HRQoL. Therapies aimed at reducing the number of days on PS may be beneficial for improving patients' HRQoL. (*Clin Ther*. 2018;40:1878−1893) © 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Key words: intestinal failure, parenteral support, short bowel syndrome, utility study, United Kingdom.

INTRODUCTION

Intestinal failure (IF) has been defined as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth."[1] IF is refined into 3 categories: type 1, acute; type 2, prolonged acute; and type 3, chronic.[2] The most frequent mechanism of IF is short bowel syndrome (SBS) in which functional small intestine length is typically <200 cm[3] and is the result of an intestinal resection. The prevalence of SBS in Europe is estimated at 1.4 per

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million, although it is recognized to vary widely, from 0.4 per million in Poland to 30 per million in Denmark, and these variations may be due to differences in the availability of intestinal rehabilitation centers.[4]

The causes of SBS in adults are most frequently mesenteric ischemia and Crohn's disease.[5] SBS can be categorized according to anatomy and pathophysiologic consequences (eg, without colon in continuity).[3] Patients with SBS frequently experience debilitating symptoms associated with their underlying condition, including weight loss, lethargy, diarrhea, excessive stoma losses, dehydration, incontinence, stoma leakage, and abdominal pain.[6]

Treatment of chronic IF requires complex technologies along with multidisciplinary input and expertise,[3] of which home-based intravenous supplementation (called parenteral support [PS] or parenteral nutrition) is a central component. The specific components of PS will vary according to the individual patient's macronutrient, micronutrient, and fluid requirements. PS is administered intravenously into a central venous catheter.[7] Individuals with chronic or type 3 IF[2] can be trained to self-administer PS at home, usually overnight.[7] When this approach is not possible, a carer, family member, or home care nurse can administer PS. The levels of specific nutrients and fluid volumes needed by individual patients are based on a formal nutrition and fluid balance assessment and are primarily determined by the length of residual healthy small bowel and the presence of disease in the remnant small bowel that may further impair absorption; thus, individuals with less small bowel remaining tend to need more PS administered over an increasing number of nights per week.[3]

It is established that patients with SBS-IF have a reduced health-related quality of life (HRQoL) as a result of their underlying condition and need for PS.[8,9] Furthermore, the need for long-term PS can lead to morbidity and, occasionally, mortality, as a result of complications related to the central venous catheter (eg, infections and/or thrombosis), liver disease, dehydration, and renal failure.[7] These complications can lead to recurrent hospital admissions, further affecting an individual's HRQoL and overall anxiety related to their condition.[7-9] Overall, however, home PS offers life-saving therapy and the ability to receive treatment at home.

Novel therapeutic options have been developed recently to reduce or even obviate PS requirements in SBS-IF; these options include surgical procedures such as transplantation and small bowel lengthening, as well as medical therapies aimed at improving the absorptive capacity of the residual small bowel.[7] Of the latter, a long-acting analogue of glucagon-like peptide 2 (teduglutide) has been shown in recent studies to reduce PS requirements in individuals with SBS-IF.[10] Cost-effectiveness analyses of such therapies are required to inform resource allocation decisions in health care.[11] Economic-related studies include the development of an algorithm by which to estimate utility scores from a patient-completed SBS-quality of life measure (SBS-QoL),[12] home- versus hospital-administered PS,[13] parenteral and enteral route of administration,[14] and collection of utility values associated with PS in Canadian patients with SBS.[15] Ideally, utilities would be obtained directly from patients by using measures such as the Euro-QoL 5D descriptive system (EQ-5D). SBS-QoL patient data from clinical trials could also provide utilities when using the published algorithm.[12] However, it would be very challenging to capture sufficient data to describe the nature of every model state when assessing the number of days on PS, especially given the rarity of the disease. The aims of the present study were as follows: first, to develop bespoke health state vignette descriptions of states for numbers of days on PS in SBS; and second, to obtain UK utility weights for these health states by using a time trade-off (TTO) preference elicitation technique.

PATIENTS AND METHODS
Study Design

Evaluation of cost-effectiveness is commonly assessed in terms of quality-adjusted life years, which are the product of HRQoL and survival. In the United Kingdom, the National Institute for Health and Care Excellence recommends that HRQoL be expressed as a preference-weighted index, preferably using the EQ-5D.[16] However, EQ-5D data were not available to assess utilities associated with PS and SBS health states. This study was designed to capture HRQoL weights (utilities) for estimating quality-adjusted life years associated with PS in SBS and to meet the requirements of health technology assessments as far as possible (eg, as discussed by the National Institute for Health and Care Excellence[17]).

Health states (vignettes) were first developed by using recognized methods[18] and are described in the following sections. The valuation sample comprised a convenience sample of 100 adults of the general

public in the United Kingdom who completed a TTO-based valuation exercise to elicit utility values for the 8 health state vignettes. A sample of 100 participants provides 100 ratings and 100 valuations for each of the 8 health states. An overview of the methods is provided in Figure 1.
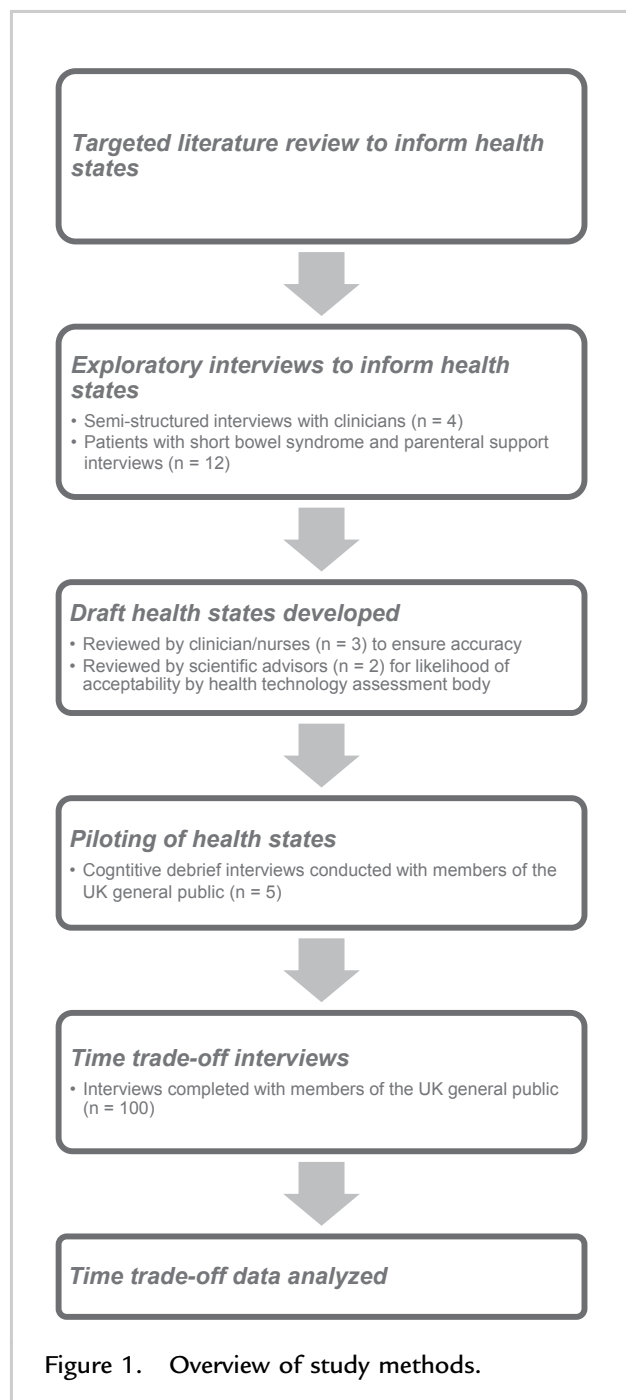

Figure 1. Overview of study methods.

The flowchart contains the following steps:

Targeted literature review to inform health states

↓

Exploratory interviews to inform health states
- Semi-structured interviews with clinicians (n = 4)
- Patients with short bowel syndrome and parenteral support interviews (n = 12)

↓

Draft health states developed
- Reviewed by clinician/nurses (n = 3) to ensure accuracy
- Reviewed by scientific advisors (n = 2) for likelihood of acceptability by health technology assessment body

↓

Piloting of health states
- Cognitive debrief interviews conducted with members of the UK general public (n = 5)

↓

Time trade-off interviews
- Interviews completed with members of the UK general public (n = 100)

↓

Time trade-off data analyzed

Health State Development

Health states were developed from 3 sources: a literature review and interviews with patients and health care professionals (HCPs).

Targeted Literature Review

A targeted literature review was undertaken to identify the impact of SBS on patients' HRQoL. This review comprised a search in EMBASE and MEDLINE for English language articles published in the last 10 years (conducted July 2015). Key words included *quality of life, coping, short bowel syndrome*, and other related terms (see Supplemental Material Tables 1 and 2 in the online version at doi:10.1016/j.clinthera.2018.09.009). Searches yielded 241 hits, with an additional 2 hits derived from Google Scholar. After excluding duplicates, 170 abstracts were reviewed for eligibility; studies that referred to QoL or EQ-5D domains were included, and pediatric studies were excluded. Twelve studies met the inclusion criteria, and the full-text articles were retrieved. Three of these articles were excluded after full article review because they were considered insufficiently relevant: one related to algorithm development,[12] and two related to the development of instruments to assess home PS[19] and pump types.[20] Figure 2 presents a description of the literature review process.

The remaining articles provided useful information regarding the burden of SBS and PS. Studies highlighted the impact of home PS; that is, it provided energy for daily activities but patients were also affected by length of infusion schedules,[21] with night infusions potentially disrupting sleep.[22] Studies outlined the burden of symptoms such as severity of gastrointestinal symptoms, fatigue, and diarrhea,[21] complications of PS,[23] and that patients with SBS had more severe fatigue and symptom severity compared with patients with inflammatory bowel disease.[24] Studies identified the psychosocial burden, including worry about the risk of catheter-related infections, general emotional problems, and disruption to social activities.[23,25−27] Compared with findings from the general population, HRQoL was impaired on most of the 8 domains of the 36-Item Short Form Health Survey questionnaire (in 6 dimensions[24] and 7 dimensions[28]). Affected domains of HRQoL are reflected in an article outlining the SBS-QoL measure: general well-being, everyday activities, working-life,

Figure 2.   Description of literature review process.
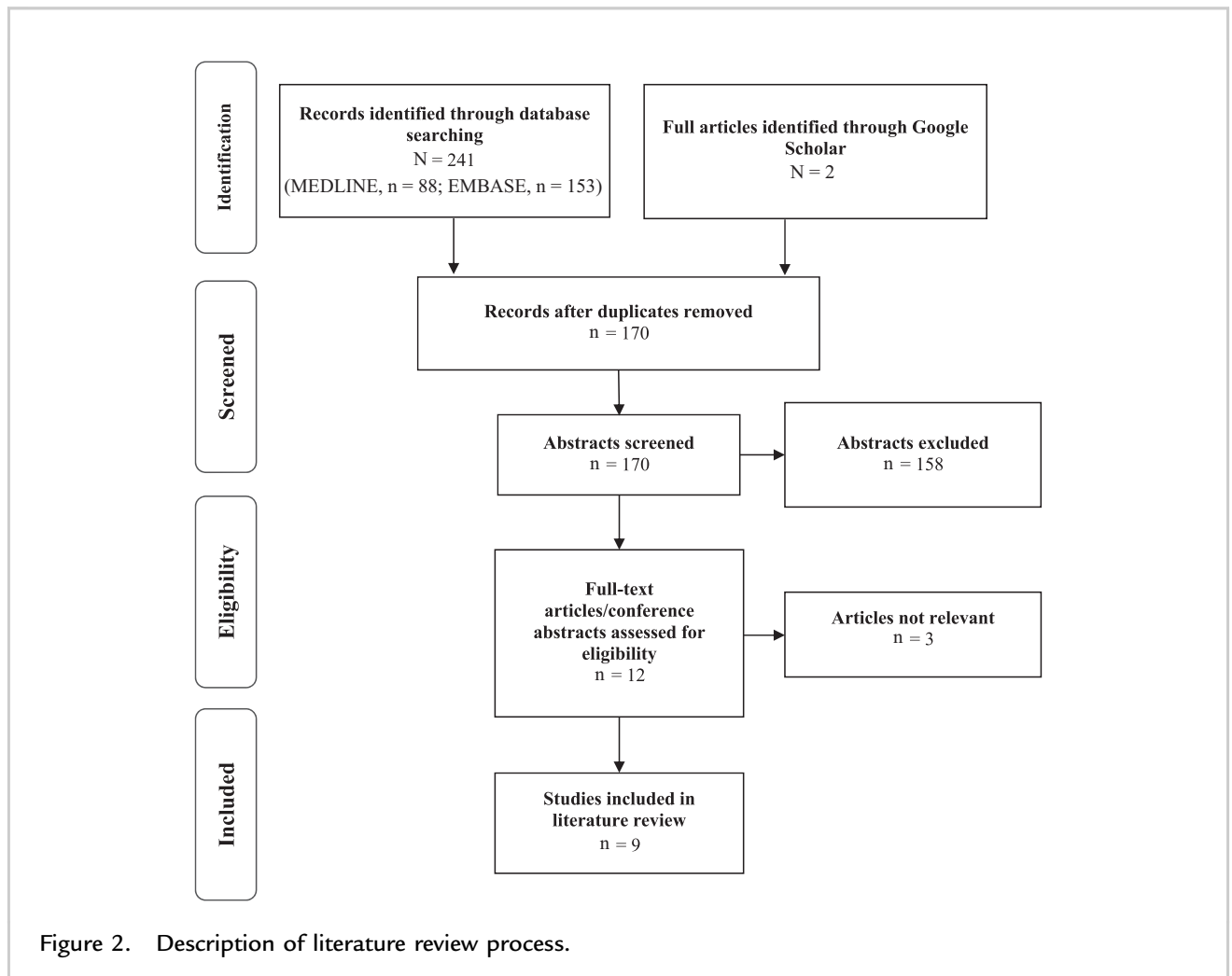
leisure activities, social life, energy level, physical health, mobility and self-care activities, pain, diet, eating and drinking habits, emotional life, sleep, gastrointestinal symptoms, fatigue and weakness, diarrhea, skeleton and muscle symptoms, discomfort and other symptoms.[6]

Patient Interviews

Patients from a patient support group were asked to comment on an interview guide developed for this study to help ensure that language was appropriate for the patient population. Patients with SBS and currently receiving home PS were then recruited from an outpatient clinic in the United Kingdom. All procedures were performed in accordance with the ethical standards of the national research committee (for patients recruited at clinic, reference no. 15/NW/

0576). Informed consent was obtained in writing from all individual participants included in the study.

An invitation letter was sent to patients before their appointment, and they were asked at the clinic if they wished to participate. If they were amenable, written consent was recorded by a clinician. A purposive sampling procedure was used to obtain a cross-section of the population including patients of different ages, sex, duration, and number of nights on PS (such as that described by Fade and Swift[29]).

Twelve patients completed in-person interviews with an interviewer using a semi-structured interview schedule. These interviews were transcribed verbatim, and coding was managed by using Atlas.Ti scientific software version 7 (ATLAS.ti Scientific Software Development GmbH, Berlin, Germany; 2013). A thematic approach to analysis was undertaken and

focused on patients' experience of SBS and PS and the impact on their daily lives. Data from the patient interviews will not be made available.

HCP Interviews

HCPs who regularly worked with UK patients with SBS were invited to take part in a telephone interview (the authors of the present article were not interviewed). Four interviews were conducted using a semi-structured interview guide. These were audio recorded, and written summaries were produced. The aim of the first 2 interviews was to understand the burden of SBS on patients; the aim of the third and fourth interviews was to understand how HRQoL was related to the number of days on PS.

Draft Health State Development

Information from the literature review and patient and HCP interviews were used to develop the first draft of the health state vignettes. These health states included 8 attributes. The first 3 described the condition, symptoms, and treatment. The next 5 attributes described the typical HRQoL effects of a person with SBS in the 5 EQ-5D domains (mobility, self-care, usual activities, pain or discomfort, anxiety, or depression). These were structured on the EQ-5D format to maintain some consistency with the preferred instrument of the National Institute for Health and Care Excellence.[17] Eight health states corresponded to 0 days on PS (having been weaned off PS) and 1 to 7 days of PS per week. Because the focus was on the number of days of PS, it was decided that health states should exclude specific reference to stoma use.

Draft Health State Review

The first draft health states were reviewed by 3 HCPs for accuracy and clinical validity during telephone interviews. These interviews were conducted with 2 clinicians who took part in the earlier interviews and an experienced nurse who was not previously interviewed, and who had particular experience with patients on fewer days of PS. These interviews were audio-recorded and summarized.

The HCPs generally believed that the draft health states characterized the impact of SBS on HRQoL and made some minor suggestions to help improve their accuracy. They appreciated the need to present a "typical patient" when in actuality there is underlying variability in conditions leading to SBS and the variations in types of PS needed. Views varied regarding the duration of PS administration; thus, due to the nurse's greater experience with the patients on fewer days PS and for methodologic reasons (ie, comparison between states not being affected by length of time on PS), it was agreed to have consistent description of 10 to 14 hours across all days on PS. This range of hours was agreed to be a reasonable average across patients with SBS.

Cognitive Interviews of Health States

Following the health state revisions, the second version of the health states was assessed via cognitive interviews with 5 members of the general public. All procedures were performed in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained in writing from all individual participants included in the study. The aim of these face-to-face interviews was to assess the interpretation of the concepts, comprehension of wording, and rating of the health states using the EQ-5D visual analog scale (VAS). Participants were also asked for general comments and any areas for improvement. The sample comprised 3 male subjects and 2 female subjects, aged 25 to 66 years (mean age, 52 years), and their own health was rated on the EQ-5D VAS at a mean of 86 (range, 70–100). The concepts and health states were found to be easily understood by all participants, and 2 participants suggested minor changes (eg, the term "irresistible" for toilet urgency was dropped; and a suggestion to replace "need to urinate" with "need to go to the bathroom" was not replaced because of the need to be specific about this aspect of the condition). The draft health states were all assigned decreased VAS scores as the number of days on PS increased, indicating that severity had been appropriately understood.

Final Health States

The third version of the health states was reviewed and agreed to by the study team and expert consultants (excluding the clinical authors of the present article) to ensure they were fit for purpose. The final 8 health states for inclusion in the study were 0 days on PS (weaned off), and each of 1 to 7 days on PS per week. These were used alongside descriptions of full health and dead states.

The draft health state vignettes were developed to provide a general description of the HRQoL of a person with SBS in the specific state relating to number of days on PS and specifically for use in economic modeling. Given the underlying variability in conditions leading to SBS and the variations in types of PS needed, these health states are inevitably a simplification, and some aspects will not apply to all patients. When the states were presented to lay members of the general public for valuation, they were not told the name of the disease. Table I presents a summary of the states.

Health State Valuation

Sample and Eligibility

A convenience sample of 100 members of the UK general public was recruited by interviewers to participate in the valuation exercise to elicit utility values for the 8 SBS health states. This exercise comprised a face-to-face interview lasting up to 1 hour using the TTO preference elicitation technique (described in the section that follows). The inclusion criteria for recruits were age ≥18 years, current resident in the United Kingdom, able to understand the survey as judged by the investigator, and able to give informed consent. Exclusion criteria included presence of an acute illness or cognitive impairment that in the opinion of the investigator would interfere with the study requirements and an inability to provide informed consent.

Four trained field interviewers based in different UK locations (Bristol, Warwickshire, and London) recruited participants with the aim to reflect age and ethnic diversity. Study details were given to potential participants. All procedures were performed in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Willing individuals provided written informed consent before data collection, and they were reimbursed for their time (£25 per individual).

Procedures

The following data collection procedures were undertaken. First, participants completed a sociodemographic form (eg, age, sex, education). Second, participants completed the 5-level EQ-5D instrument, including the visual analog question asking for rating of their health.[30] Third, participants rated the

SBS PS health states using the VAS. Each of the 8 health states were printed on individual cards (along with full health and dead states). The name of the health states had been replaced with a symbol to avoid any reference to the condition. Using an enlarged copy of the EQ-5D VAS scale, participants were presented with 1 health state at a time in a random order and asked to rate each of the health state vignettes. This task was designed to familiarize participants with the health states vignettes. Participants placed the cards on a 100-point VAS according to their opinion. A rating of 100 was defined to participants as "the best possible state of health imaginable." The values given to each health state were documented, and participants were given the option to revise the values at the end of the exercise.

Finally, participants provided ratings for each of the 8 health states using the TTO technique and a standard prop. Here, the same health state cards were presented in a random order. Randomization of states follows recommended procedures and reinforces the validity of results (eg, any trend is in spite of the sequence of administration).[31] For states regarded as better than being dead, respondents were presented with a series of pairwise choices and asked to choose between living in the health state for 10 years or living in a state of full health for ≤10 years. Time in full health was varied in 6-month increments until the participant was indifferent between the 2 choices. The amount of time in the state that someone is willing to trade is taken to indicate the value or utility of the state. The TTO method, in deriving utility values based upon subjects' responses to decision scenarios, was specifically developed for use in health care.[32] A 10-year time horizon was selected to provide a consistent time frame for all respondents and has been commonly used in previous studies in line with initial EQ-5D valuation work[33]; it does not reflect life expectancy associated with SBS or PS (for which life expectancy is principally determined by the disease underlying SBS). Any states that were valued as worse than dead were valued by using Lead-Time methods using a standard lead-time TTO (LT-TTO) board. LT-TTO is another variant of TTO in which each option has an additional 10 years in full health at the start before proceeding to the 10 years in the ill health state or ≤10 years in full health. This method allows for utility scores of between 0 and −1 to be elicited.[34] An alternative to LT-TTO was previously used comprising 2 tasks: one for states

Table I.   Final health state categories.

1. Condition description	• Full health: You do not have any illnesses
	• 0 days on PS (weaned off): You have a condition where you need to pay attention to your fluid and nutrient intake
	• 1—7 days on PS: You have a condition where you need to pay attention to your fluid and nutrient intake and cannot absorb nutrients normally
2. Symptom description	• 0 days on PS (weaned off): You may feel dehydrated, weak, and tired. You sometimes have diarrhea and a sudden need to have a bowel movement
	• 1—3 days on PS: (as per 0 days) and you have to limit your food and drink intake*
	• 4—7 days on PS: (as per 1—3 days) and minor change from "you *sometimes have* diarrhea" to "you *have* diarrhea"
3. Treatment description	• Full health: You are not receiving any treatments
	• 0 days on PS (weaned off): You take medication to treat your diarrhea. You have a daily allowance in the amount you can drink. You have a diet that needs to be high in fat.† Sometimes you need to drink I L of a glucose-saline drink, which tastes a bit like seawater
	• 1—7 days on PS: You are administered nutrient solution through a tube in your chest for 10—14 hours on [number] days a week. This supplements the food and drink that you eat normally
4. Mobility	• Full health: You have no physical problems walking about
	• 0 days (weaned off)—7 days on PS: You have no physical problems walking about
5. Self-care	• Full health: You have no problems washing and dressing yourself
	• 0 days on PS (weaned off): You have no problems washing and dressing yourself
	• 1—7 days on PS: (in addition to 0 days) you need to be cautious when washing yourself to minimize risk of infection to your tube. You need to get up in the night to urinate on your [number] days of treatment
6. Usual activities	• Full health: You have no problems in completing your usual activities
	• 0 days on PS (weaned off): Due to diarrhea and fatigue, you are sometimes limited in your usual activities
	• 1—3 days on PS: (in addition to 0 days) and due to having a tube, you are unable to do physical exercise.‡ Due to time for medical care, you are sometimes limited in your daily activities on your [number] days of treatment
	• 4—5 days on PS: (as per 1—3 days) and minor change from "you *are sometimes* limited" to "*you are limited* in your daily activities on your [number] days of treatment"
	• 6—7 days on PS: (as per 4—5 days) and it is difficult to take part in spontaneous activities
7. Pain/discomfort	• Full health: You have no pain or discomfort
	• 0 days (weaned off)—7 days on PS: You have pain if you eat fibrous food
8. Anxiety/depression	• Full health: You are not anxious or depressed
	• 0 days on PS (weaned off): You are glad that you do not need to receive nutrients through a tube in your chest

(*continued on next page*)

Table I (continued)

	• 1–5 days on PS: You sometimes worry about getting an infection and your long-term health. You feel anxious in case you need to get to a toilet quickly. You sometimes feel your treatment is a bit difficult to cope with
	• 6 days on PS: (as per 1–5 days) and you value having 1 day per week without having treatment
	• 7 days on PS: (as per 1–5 days) and you would value having 1 day per week without having treatment
Dead state	• You are dead

PS = parenteral support.

* Patients with short bowel syndrome (SBS) often have to follow a special diet, and thus "limit" is intended here to broadly refer to constraints rather than to quantity, per se.

† SBS can include patients with a colon in continuity. Such patients are advised not to have a diet high in fat.

‡ This should not be taken to imply that SBS patients receiving PS are unable to exercise, although they are limited during the time they are connected to PS. Patients' general ability to exercise are more likely to be associated with the conditions underlying SBS, and any concerns that patients might have about this topic should be discussed with their health care professional.

better than dead and another for states worse than dead. This approach has been shown to result in a discontinuity of values and 2 very different distributions of values, raising doubts about whether they can be regarded as being on the same scale.[34] The LT-TTO approach was therefore used because it provides the respondent with more years to use up and means that there is only 1 TTO task, reducing the risk of confusion.

Data Entry and Analysis

Interviewers entered the data onto a pre-prepared Excel spreadsheet (Microsoft Corporation, Redmond, Washington). Fifty percent of data entry was double-checked to verify the database before analysis (within each of the datasets provided by the 4 interviewers, data for verification was randomly selected). The utility interview data will be shared with researchers upon request. Basic descriptive analysis was undertaken using Excel to describe the study sample and for comparison versus Office of National Statistics published norms[35–37]; comparison of their health status according to the EQ-5D versus UK published norms[38]; and to report the VAS ratings of health states (range, means, and SDs) and TTO values of health states (range, means, and SDs). Analysis was confirmed independently by a second member of the study team by review of Excel analysis codes and results. Linear regression analyses

of VAS ratings and utility scores against health states were conducted in Stata version 12.1 (StataCorp, College Station, Texas). Separate models were run with health states as a continuous variable (in terms of the number of days receiving PS) and as dummy variables.

RESULTS

Participant Characteristics

Table II displays the sample characteristics of the 100 members of the UK general public who were interviewed and comparative data from the Office of National Statistics for a UK population.

Table III details the EQ-5D dimension reported by the study sample and the UK norms.[38] Overall, the differences were modest, although the study sample reported fewer problems than the UK general public. The sequence of most affected domains was the same: pain or discomfort had the greatest proportion, followed by anxiety or depression, mobility, and usual activities, with self-care the least affected. The mean state of health recorded on the VAS was similar to UK norms (83.25 with standard deviation of 15, vs. 82.5 with standard deviation of 17) [38].

VAS Ratings of Health States

Table IV shows the mean scores from the VAS ratings of the health states, which had been administered in random order. The highest mean

Table II. Participant characteristics.

Characteristic	N = 100	Population[*]
Sex		
Male	33 (33%)	31,793,606 (49.2%)
Female	67 (67%)	32,803,146 (50.8%)
Age, y		
Median (mean [SD])	32 (38.04 [15.84])	40
Range	18–87	–
Ethnicity[†]		
White, British[‡]	75 (75%)	80.5%
White, other	6 (6%)	5.4%[§]
Asian/Asian British[‖]	8 (8%)	6.0%
Black British/African/Caribbean/ black, Caribbean	4 (4%)	1.1%
Mixed/multiple ethnic group[¶]	7 (7%)	1.9%
Main activity[#]		
Employed	79 (79%; of which 17% are part-time)	74%[**]
Student	11 (11%)	–
Unemployed	3 (3%)	5.1%
Retired	7 (7%)	13.1%
Self-employed	1 (1%)	–
Qualifications		
No formal qualifications	2 (2%)	22.7%
GCSE/secondary school	8 (8%)	28.6%[††]
A Levels/college	24 (24%)	15.9%[‡‡]
Undergraduate degree (BSc, BA)	36 (36%)	27.2[§§]
Postgraduate degree (e.g. masters', PhD)	29 (29%)	–
Other	1 (1%)	5.7
Marital status		
Single	40 (40%)	34.6%
Partnership	23 (23%)	0.2%[‖‖]
Married	29 (29%)	46.6%
Divorced/separated	6 (6%)	11.6%
Widowed	1 (1%)	7%
Other	1 (1%)	–

GCSE = General Certificate of Secondary Education; A Level = General Certificate of Education Advanced Level; BSc = Bachelor of Science; BA = Bachelor of Arts; PhD = Doctor of Philosophy.

[*] Ethnicity, qualifications, and marital status data from England and Wales Census data (Office for National Statistics, 2011).[35] Sex and age data from Overview of the United Kingdom (Office for National Statistics, 2015).[36] Employment data from UK Statistical Bulletin (Office for National Statistics, 2015).[37]

[†] Office of National Statistics (ONS) percentages calculated from equivalent categories as per footnotes ‡ through ¶.

[‡] White, British calculated by combining: white, English; white, Welsh; white, Scottish; and white, Northern Irish.

[§] Calculated from the ONS groups: white, Irish; white, Gypsy or Irish Traveller; white, other white.

[‖] Asian/Asian British group calculated by combining: Asian/Asian British, Indian; Asian/Asian British, Pakistani; Asian/Asian British, Bangladeshi; and Asian/Asian British, Chinese.

[¶] Mixed/multiple ethnic group calculated by combining: mixed/multiple ethnic group, white and black Caribbean; mixed/multiple ethnic group, white and Asian; and mixed/multiple ethnic group, other.

[#] One participant responded that they were both employed full-time and a student.

[**] People aged 16 to 64 years, part-time and full-time combined, students in employment included.

[††] Level 1 (1–4 GCSEs or equivalent) and Level 2 (5 GCSEs or equivalent) qualifications combined.

[‡‡] Apprenticeships and Level 3 (2 + A Levels or equivalent) qualifications combined.

[§§] Level 4 qualifications or above (bachelor's degree or equivalent, and higher qualifications).

[‖‖] Registered same-sex civil partnership (there is no other partnership category in ONS; anyone not married but living with a partner would possibly be considered "single").

Table III. Comparison of health status of the study sample versus UK published norms according to EuroQol-5 dimensions.

Dimension	Study Sample* (N = 100)		UK Norms[†] (N = 3395)	
	Any Problem %	Ranking	Any Problem %	Ranking
Mobility	14	3	18.4	3
Self-care	2	5	4.2	5
Usual activities	13	4	16.3	4
Pain/discomfort	27	1	33.0	1
Anxiety/depression	19	2	20.9	2
Any dimensions	36		43.1	

* Study sample using the 5-level EuroQoL 5 dimension.
[†] UK norms using the 3-level EuroQoL 5 dimension.

(SD) value is for the 0 days on PS at 0.70 (16), with the lowest value for 7 days on PS at 0.26 (18). The ratings of the health states show a decline according to number of days on PS. The largest decline between the mean ratings of consecutive states was from 0 days (weaned off) to 1 day (declined by 0.13). The decline in mean ratings between the other consecutive states ranged from 4 to 7 points.

The results of the regression models of VAS ratings of health states, predicted by health states in terms of number of days receiving PS as a continuous variable and as dummy variables, are shown in Tables V and VI, respectively. The continuous variable model showed a significant difference in VAS ratings across the health states, whereby for every 1 additional day receiving PS there was an estimated 5.96-point reduction in VAS ratings ($P < 0.001$). The findings from the dummy variable model are in agreement: relative to zero days, all other numbers of days receiving PS are associated with significant reductions in VAS ratings (–13.79 [1 day] to –44.81 [7 days]; $P < 0.001$). There is limited literature by which to

Table IV. Visual analog scale rating of health states (with full health at score 100) (N = 100).

Health State	Mean (SD)	Difference Between Consecutive States	Minimum Rating Given	Maximum Rating Given
0 days on PS (weaned off)	0.70 (0.16)		8	95
1 day on PS	0.57 (0.17)	0.13	12	90
2 days on PS	0.50 (0.17)	0.07	5	90
3 days on PS	0.45 (0.18)	0.05	3	95
4 days on PS	0.39 (0.17)	0.06	2	80
5 days on PS	0.35 (0.18)	0.04	0*	95
6 days on PS	0.30 (0.18)	0.05	0[†]	90
7 days on PS	0.26 (0.18)	0.04	0[‡]	90

PS = parenteral support.
* One participant rated 5 days on PS as equal to death.
[†] Four participants rated 6 days on PS as equal (n = 3) or worse (n = 1) than death.
[‡] Seven participants rated 7 days on PS as equal (n = 4) or worse (n = 3) than death.

Table V. Results of simple linear regression models of visual analog scale ratings of health states against the number of days receiving parenteral support (PS) of the health state (as a continuous variable).

Model	Regression Estimates		
	Beta-Coefficient (SE)	CI	P
Days on PS	−5.96 (0.27)	−6.49 to −5.44	<0.001
Intercept	64.85 (1.12)	62.64 to 67.05	<0.001

Table VI. Results of multiple linear regression models of visual analog scale ratings of health states against the number of days receiving parenteral support (PS) of the health state (as dummy variables; reference group = 0 days on PS).

Model	Regression Estimates		
	Beta-Coefficient (SE)	CI	P
0 days on PS (weaned off)	Ref	Ref	Ref
1 day on PS	−13.79 (2.44)	−18.59 to −8.99	<0.001
2 days on PS	−20.03 (2.44)	−24.83 to −15.23	<0.001
3 days on PS	−25.69 (2.44)	−30.49 to −20.89	<0.001
4 days on PS	−31.26 (2.44)	−36.06 to −26.46	<0.001
5 days on PS	−35.62 (2.44)	−40.42 to −30.82	<0.001
6 days on PS	−40.77 (2.44)	−45.57 to −35.97	<0.001
7 days on PS	−44.81 (2.44)	−49.61 to −40.02	<0.001
Intercept	70.47 (1.73)	67.08 to 73.86	<0.001

assess meaningful change in VAS ratings. One study using a respiratory questionnaire and a feeling thermometer VAS suggests that a change of 5 to 8 points out of 100 could be taken to be clinically important in patients.[39] Although not strictly comparable with members of the public, this finding could nonetheless provide some indication that the VAS reductions are meaningful.

Health States Utility Scores

Table VII presents the results of the mean TTO utility values elicited for each of the 8 health states (these were administered in random order in interviews). The highest mean (SD) value is for the 0 days on PS (0.82 [0.22]), with the lowest value for the state 7 days on PS (0.36 [0.35]). The ratings of the health states show a decline by number of days on PS. However, the largest decline was between 5 days to 6 days on PS (declined by 0.10), which is different from the largest decline by ratings using the VAS (as reported above, this was 0−1 days). The decline in mean utilities between the other consecutive states ranged from a difference of 0.04 to 0.07. In the wider literature, a difference or change of ≥ 0.05 has been used as a guideline for clinically important difference in TTO scores.[40,41] This outcome, then, would suggest that all changes, apart from 0 days to 1 day on PS, could be considered meaningful, albeit based on group mean scores provided by members of the public. Three participants valued one or more health states as worse than death.

The results of the regression models of utility scores, predicted by health states in terms of number of days receiving PS as a continuous variable and as dummy variables, are shown in Tables VIII and IX, respectively. The continuous variable model shows that the number of days receiving PS is significantly associated with utility scores. For every 1 additional day receiving PS, there is an estimated 0.07 reduction in utility scores ($P < 0.001$).

Table VII. Health states utility scores (N = 100).

Health State	Mean (SD)	Change Between Consecutive States	Minimum Rating Given	Maximum Rating Given	No. of Participants Valuing State Worse Than Death
0 days on PS (weaned off)	0.82 (0.22)		−0.48*	1	1
1 day on PS	0.78 (0.23)	0.04	−0.48	1	1
2 days on PS	0.72 (0.23)	0.06	−0.48	1	1
3 days on PS	0.65 (0.27)	0.07	−1	0.98	1
4 days on PS	0.58 (0.31)	0.07	−1	1	2
5 days on PS	0.51 (0.33)	0.07	−1	0.98	2
6 days on PS	0.41 (0.34)	0.10	−1	0.98	3
7 days on PS	0.36 (0.35)	0.05	−1	1	2

PS = parenteral support.
* One participant rated all states, including 0 days, as worse than death. Also, 3 participants rated all health states the same (each valued all health states at 0.98).

Table VIII. Results of simple linear regression models of utility scores for the health states against the number of days receiving parenteral support (PS) of the health state (as a continuous variable).

Model	Regression Estimates		
	Beta-Coefficient (SE)	CI	P
Days on PS	−0.07 (0.004)	−0.08 to −0.06	<0.001
Intercept	0.84 (0.02)	0.81 to 0.88	<0.001

Table IX. Results of multiple linear regression models of utility scores for the health states against the number of days receiving parenteral support (PS) of the health state (as dummy variables; reference group = 0 days on PS).

Model	Regression Estimates		
	Beta-Coefficient (SE)	CI	P
0 days on PS (weaned off)	Ref	Ref	Ref
1 day on PS	−0.04 (0.04)	−0.12 to 0.04	0.286
2 days on PS	−0.10 (0.04)	−0.18 to −0.02	0.013
3 days on PS	0.17 (0.04)	−0.25 to −0.09	<0.001
4 days on PS	−0.24 (0.04)	−0.32 to −0.16	<0.001
5 days on PS	−0.32 (0.04)	−0.40 to −0.23	<0.001
6 days on PS	−0.41 (0.04)	−0.49 to −0.33	<0.001
7 days on PS	−0.46 (0.04)	−0.54 to −0.38	<0.001
Intercept	0.82 (0.03)	0.76 to 0.88	<0.001

The dummy variable model estimates that relative to zero days, ≥2 days show a significant reduction in utility scores (–0.10 [2 days] to –0.46 [7 days]; $P < 0.013$). There was no significant difference between utility scores for 0 and 1 day receiving PS ($P = 0.286$).

DISCUSSION

To the best of our knowledge, this study is the first to show that utilities are perceived by the general public to be associated with different levels of PS on the HRQoL of individuals with SBS in the United Kingdom. Significantly, the study reported a decline in utility values measured by TTO with increased number of days on PS, with 7 days on PS showing the largest disutility and 0 days on PS the smallest disutility from full health. Decline in TTO utility values was confirmed by a corresponding decline in the health states rating by using the VAS and in the regression analyses undertaken. When using dummy variables, the utility scores only exhibited a significant reduction with each additional day of PS from 2 days or more. These data suggest that any treatment which may help reduce the number of days on PS could be seen as beneficial for the HRQoL of patients with SBS receiving PS and may be used to assess cost-effectiveness of such a treatment.

This monotonic decline is similarly reflected in a Canadian utility study.[15] In that study, 799 valid respondents (of 1277 participants) evaluated 3 health states each by a web-based TTO study. These states were similarly defined by numbers of days on PS (0–7 days), with the 7 days on PS divided into low and high liter amounts of PS administered. The largest disutility was 7 days on PS high liter volume valued at 0.39, with the smallest disutility being 0 days on PS at 0.74. Thus, despite the differences in methods, the findings from the Canadian study were broadly in keeping with the present UK study. The UK study shows this relationship is monotonic across the range of PS, which has important implications for the benefits of interventions.

There are study limitations that should be considered. First, the TTO study sample was younger, with more female subjects, and 9% more had an undergraduate degree compared with the general UK population. However, the ethnicity, qualifications, and marital status data came from a 2011 census that may have changed since that time. The modestly better health of the sample according to EQ-5D scores may reflect the slightly younger study population compared with general population norms. Second, the 10-year time horizon does not reflect any specific life expectancy associated with PS and SBS because of the heterogeneity of the conditions underlying SBS. Nonetheless, compared with longer time horizons, 10-year horizons could result in higher or less conservative utility values because of increased loss aversion to the amount of time traded off.[42,43] There is no apparent consensus in the literature about the right time horizon for health states. Although states could have been valued differently with a different time horizon in this study, it may be reasonable to consider that the relative differences between the states are unlikely to change.

A vignette approach has previously been criticized because the content is often not empirically determined with input from patients and clinicians and is not usually formally validated.[18] If the vignettes are poorly designed, they can lead participants to focus on very specific aspects of HRQoL, which can cause exaggerated differences in the resulting utilities. However, this study undertook several steps to ensure robust vignette development in the drafting, review, and finalization. The symptoms described were those reported for a "typical" patient; however, it was clear from the literature review and patient and HCP interviews, that there is no such thing as a typical SBS patient, because of the underlying heterogeneity of conditions and differences in nutritional requirements. More states could have been valued to have allowed for such heterogeneity. As it was, we attempted to keep health state descriptions as simple as possible. In addition, because of recruitment difficulties, no interviews were conducted with patients who had been weaned off or received only 1 or 2 days of PS. Therefore, the vignettes corresponding to these health states relied upon data from the literature review and HCP interviews only. There is some literature showing discordance between patient and HCP perceptions in other conditions and clinical contexts,[44–48] and thus it is possible that patients with SBS who had been weaned off PS or had received only 1 or 2 days of PS may have different views than the information provided in the literature or HCP interviews. Furthermore, in the absence of direct experience with new therapies that may help maintain a patient's nutritional balance while reducing the need for PS, it is possible that patients may feel

reassured by continued PS knowing their nutritional requirements are being met. Review of draft health states was conducted with HCPs and members of the public, but it may have been useful to have included patients. Finally, participants may have made assumptions about the condition and treatment beyond the information that was provided in the vignettes, which could influence their responses (eg, how having a tube in their chest might feel and affect daily activities). However, the participants in the cognitive interviews were specifically asked if there were any ways in which the health states could be improved, and none indicated need for additional information. Furthermore, it is not common practice to assess how participants reach their judgments when providing their responses during TTO interviews.

CONCLUSIONS

This study has produced utility weights from a UK general population sample for states associated with PS in SBS and, to do so, used a robust approach to vignette development. The findings show how utility values were progressively worse as the number of days on PS increased.

APPENDIX A. SUPPLEMENTARY DATA

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.clinthera.2018.09.009.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary Material Table 1. Search strategy in Embase

	Database: Embase <1974 to 30 June 2015>	
1	QOL.tw.	(39442)
2	(value adj2 life).tw.	(749)
3	"Value of Life"/	(116895)
4	"Quality of Life"/	(287073)
5	Quality of Life.tw.	(249117)
6	life quality.tw.	(7506)
7	HRQL.tw.	(3760)
8	HRQoL.tw.	(13351)
9	health related quality of life.tw.	(34461)
10	patient$ attitude$.tw.	(2741)
11	patient attitude/	(51425)
12	attitude to health/	(86802)
13	(attitude adj3 health).tw.	(1227)
14	well$ being.tw.	(55897)
15	wellbeing/	(37644)
16	cost of illness/	(15556)
17	Emotion/	(78073)
18	(burden adj3 (illness or disease$)).tw.	(24696)
19	coping behavior/	(38338)
20	(cope or coping).tw.	(71742)
21	(value adj2 life).tw.	(749)
22	psychological$ adapt$.tw.	(663)
23	(psychological$ adj3 adapt$).tw.	(1175)
24	or/1—23	(792065)
25	short bowel syndrome$1.tw.	(3205)
26	short gut syndrome$1.tw.	(365)
27	short intestinal syndrome$1.tw.	(3)
28	short intestine syndrome$1.tw.	(35)
29	chronic intestinal failure.tw.	(111)
30	if type 3.tw.	(4)
31	if type iii.tw.	(5)
32	short bowel syndrome/	(4356)
33	or/25—32	(5103)
34	24 and 33	(357)
35	limit 34 to (English language and last 10 years)	(191)
36	conference.so.	(1926416)
37	35 not 36	(153)

Supplementary Material Table 2. Search strategy in Medline

	Database: Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® <1946 to Present> [Present was 01 July 2015]	
1	QOL.tw.	(22113)
2	"Value of Life"/	(5451)
3	"Quality of Life"/	(127151)
4	Quality of Life.tw.	(167265)
5	life quality.tw.	(4138)
6	HRQL.tw.	(2579)
7	HRQoL.tw.	(8786)
8	health related quality of life.tw.	(25458)
9	patient$ attitude$.tw.	(2041)
10	Attitude to Health/	(74599)
11	well$ being.tw.	(44383)
12	"Cost of Illness"/	(19159)
13	Emotions/	(45846)
14	(burden adj3 (illness or disease$)).tw.	(17382)
15	(burden adj3 illness).tw.	(1870)
16	Adaptation, Psychological/	(77385)
17	(cope or coping).tw.	(55257)
18	(patient$ adj10 (cope or coping)).tw.	(7386)
19	(value adj2 life).tw.	(589)
20	psychological adaptation.tw.	(432)
21	psychological$ adapt$.tw.	(499)
22	(psychological$ adj3 adapt$).tw.	(856)
23	or/1—22	(475533)
24	short bowel syndrome$1.tw.	(2458)
25	short gut syndrome$1.tw.	(276)
26	short intestinal syndrome$1.tw.	(3)
27	short intestine syndrome$1.tw.	(26)
28	chronic intestinal failure.tw.	(74)
29	if type 3.tw.	(2)
30	if type iii.tw.	(2)
31	short bowel syndrome/	(2455)
32	or/24—31	(3543)
33	23 and 32	(220)
34	limit 33 to (English language and last 10 years)	(88)