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Published in:
BMJ Open

DOI (link to publication from Publisher):
10.1136/bmjopen-2021-058500

Publication date:
2022

Document Version
Publisher's PDF, also known as Version of record

BMJ Open

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To cite: Halling CMB, Gudex C, Perner A, *et al*. Public versus patient health preferences: protocol for a study to elicit EQ-5D-5L health state valuations for patients who have survived a stay in intensive care. *BMJ Open* 2022;**12**:e058500. doi:10.1136/bmjopen-2021-058500

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-058500).

Received 19 October 2021
Accepted 06 May 2022

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ABSTRACT

Introduction The value set used when calculating quality-adjusted life-years (QALYs) is most often based on stated preference data elicited from a representative sample of the general population. However, having a severe disease may alter a person's health preferences, which may imply that, for some patient groups, experienced QALYs may differ from those that are estimated via standard methods. This study aims to model 5-level EuroQol 5-dimensional questionnaire (EQ-5D-5L) valuations based on preferences elicited from a sample of patients who have survived a stay in a Danish intensive care unit (ICU) and to compare these with the preferences of the general population. Further, the heterogeneity in the ICU patients' preferences will be investigated.

Methods and analysis This valuation study will elicit EQ-5D-5L health state preferences from a sample of 300 respondents enrolled in two randomised controlled trials at Danish ICUs. Patients' preferences will be elicited using composite time trade-off based on the EuroQol Valuation Technology, the same as that used to generate the EQ-5D-5L value set for the Danish general population. The patient-based and the public-based EQ-5D-5L valuations will be compared. Potential underlying determinants of the ICU preferences will be investigated through analyses of demographic characteristics, time since the ICU stay, self-reported health, willingness to trade-off length of life for quality of life, health state reference dependency and EQ-5D dimensions that patients have experienced themselves during their illness.

Ethics and dissemination Under Danish regulations, ethical approval is not required for studies of this type. Written informed consent will be obtained from all patients. The study results will be published in peer-reviewed scientific journals and presented at national and international conferences. The modelling algorithms will be publicly available for statistical software, such as Stata and R.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ EuroQol's recommendations for the EuroQol Valuation Technology (EQ-VT) protocol will be followed with a few exceptions due to practical limitations when enrolling patients.
⇒ To limit the interview burden for the patient and to allow time for additional questions, the scope of the valuation study is limited to composite time trade-off and excludes the discrete choice experiment part of the EQ-VT protocol.
⇒ Additional questions are included to offer possible explanations for the potential differences between the preferences of the intensive care unit patients and the general population.

INTRODUCTION

Economic evaluations in the form of cost–utility analyses are increasingly used in the prioritisation of healthcare resources. The health outcome in cost–utility analyses is typically measured by quality-adjusted life-years (QALYs) that are based on health state preferences from a representative sample of the general population.[1] The question is whether it is more appropriate to use the perspectives of the general population or that of patients who have actually experienced the condition and treatment being assessed when eliciting health state valuations.

Quality-adjusted life years

QALYs are a standardised measure in which two health dimensions are accounted for: health-related quality of life (HRQoL) and the period in which the HRQoL is experienced. This period may be the length of an intervention or the time until death. The HRQoL dimension consists of a description of a person's health state and then a preference weighting using pre-existing value sets. QALYs are calculated by multiplying the health state values by the time spent in each health state.[2]

The EQ-5D is a widely used instrument for assessing health status and is frequently used in economic evaluations.[3] The 5-level EuroQol 5-dimensional questionnaire (EQ-5D-5L) has five dimensions (mobility,

self-care, usual activities, pain/discomfort and anxiety/depression), each with five levels ranging from no problems to extreme problems, for example, from 'no problems walking' to 'unable to walk'.[4] To translate these health states into QALY weights, each health state is valued on a scale where 0 is equivalent to being dead and 1 indicates full health. The specific value assigned to each health state is based on valuations expressed by respondents using stated preference methods.

Patients in intensive care units (ICUs) to investigate empirically whether patient and public valuations differ, we select an extreme patient group whose preferences would be expected to deviate markedly from those of the general population. Survivors from a stay in the ICU constitute a patient group who has experienced life-threatening illness and invasive interventions concentrated over a short period. We focus on ICU patients as they might be better informed about living with imperfect health states and they have experienced a severe health event that may have altered their preferences for health states. This severe health event may have changed their view of which health dimensions are important for survival and quality of life, and it may also make them more/less reluctant to trade-off longevity for quality of life.

Public-based versus patient-based preferences

Most healthcare decision-making bodies, including those in Europe (eg, the National Institute for Health and Care Excellence (NICE) in the UK and the Danish Medicines Council), Australia, Asia, and North and South America,[1 5–8] recommend calculating QALYs using EQ-5D and preferences derived from a representative sample of the general population—so-called public-based preferences.[9] The most popular argument in favour of this general population approach is that health allocation decisions should be made according to the views of taxpayers who are insuring themselves against future need for healthcare and thus ultimately funding healthcare.[1 10] It is also argued that resources will be more fairly distributed with a population approach as the allocation of resources is less prone to strategic biases when all citizens can cast a vote.[11 12]

An argument against public-based preferences is that they are elicited by asking the general population to imagine health states that might be hypothetical to them, and the general population may lack adequate experience or knowledge of the health states.[1 13 14] Further, the general population approach does not take into account the possibility that patients can adapt to poor health states.[15] The general population may undervalue the possibility of adaptation and place more value on the transitional change from their current health state to the poorer health state in question.[15] Empirical studies have indicated that people in particular health states have different views of those states compared with those trying to imagine the states.[15–17] For instance, mental health tends to be undervalued compared with physical problems when uninformed preferences are used.[17] This could lead to the conclusion that patients' preferences should be used as they know how the situation will be. However, the opposite can also occur; patients may undervalue the transitional change and thereby the losses that have already taken place, and further, they may find it difficult to imagine full health.[14 15] Differences in preferences could also arise if respondents' views of health states are dependent on the state of their own health. This is often referred to as 'health state reference dependency'.[18]

A meta-analysis from 2006 found no significant differences between patient-based and public-based preferences,[19] but noted that the direction and the magnitude of the differences depended on the type of health states assessed. In contrast, a more comprehensive meta-analysis from 2010 concluded that there were indeed differences as patients valued health states higher than did the general population.[20] Several more recent studies have confirmed such differences.[12 21 22] For instance, anxiety/depression was shown to have the largest impact on quality of life for patients in a study from the UK covering eight different conditions, whereas pain/discomfort had the largest impact for the general population.[21] Ogorevc *et al*[12] reported that patients with metastatic breast cancer or rheumatoid arthritis were better able than the general population to imagine 'non-tangible' dimensions of health states (anxiety/depression and pain/discomfort).[12]

Aims and research questions

The underlying main research question of this study is: Do people who have experienced critical illness and intensive care express preferences for health states that differ from those of the general population? To examine this, we aim to (1) generate patient-specific health state valuations, (2) compare these with health state valuations from the general population and (3) investigate the differences.

Generate: This project aims to derive EQ-5D-5L valuations from the health state preferences of a sample of Danish adults who have survived critical illness and intensive care. The focus will be on measuring the patients' forward-looking preferences.

Compare: An additional aim is to compare these patient valuations with the general population valuations using the recently published Danish EQ-5D-5L value set.[23]

Investigate: We will investigate the heterogeneity in the ICU patients' valuations and explore why patient preferences may differ from those of the general public. To investigate the potential reasons for observed differences, we pursue the following four research questions:

1. Which factors influence the ICU patients' preferences for health states? Potential underlying determinants could be demographic characteristics, time since the ICU stay (to investigate adaptation and stable preferences) and self-reported HRQoL.
2. Are ICU patients more reluctant to trade-off longevity for HRQoL than the general population? If ICU

patients are more reluctant to trade-off longevity for HRQoL, does this impact the relative weighting of health states, or does it merely entail a constant change in the marginal rate of substitution between longevity and HRQoL?
3. Does 'health state reference dependency' apply to ICU patients, and do ICU patients' preferences deviate more from those of the general public on dimensions where they have gained experience through their own illness?

METHODS AND ANALYSIS

Generation of EQ-5D-5L health state valuations for ICU patients

The reporting of the EQ-5D-5L valuation study in patients will follow the CREATE checklist, which identifies the key elements that should be reported in valuation studies.[24] EQ-5D-5L health state valuations will be obtained using the EQ Valuation Technology (EQ-VT), which is based on computer-assisted face-to-face interviews and use of the composite time trade-off (cTTO),[25 26] see section 2.1.2 for more details.

Case population and sampling

This study generates EQ-5D-5L health state valuations for ICU patients based on a sample of 300 respondents from two randomised controlled trials (RCTs). The patient group will be referred to as ICU patients in the following. Inclusion criteria are patients surviving an acute ICU admission (to avoid planned ICU admissions after elective operations) who were aged 18 years or older at the time of the ICU stay, are fluent in Danish, and are cognitively able to follow the interview. Patients will be recruited from one of two RCTs conducted in Danish ICUs. One is the HOT-ICU trial that examines the benefits and drawbacks of two different oxygen targets for patients with acute hypoxic respiratory failure.[27] The HOT-ICU exclusion criteria include pregnancy, long-term mechanical ventilation, and brain death; further exclusion criteria are found in the HOT-ICU protocol.[28] The other RCT is the CLASSIC trial that examines the effects of restricted intravenous fluids vs standard care fluid therapy in patients with septic shock.[29] In the CLASSIC trial, patients are excluded if, for example, they have had septic shock for more than 12 hours at the time of screening, have life-threatening bleeding, have acute burn injury over more than 10% of the body surface area, or are pregnant; more information on the exclusion criteria are found in the CLASSIC protocol.[30] The only additional criterion to those from the RCTs is that patients with impaired cognitive function will be excluded, see section 2.1.7 for further details.

Surviving patients with valid consent will be contacted regarding participation in an EQ-VT interview 1 year after randomisation in CLASSIC or after having completed the HOT-ICU trial.[28 29 31] The randomisation of patients into the trial arms occurred early in the ICU stay. Oral consent will be obtained from patients between December 2019 and March 2022. The EQ-VT interview will be held face to face in the patient's home or at the site where they were enrolled in the trial. The EQ-VT valuation interviews are planned to take place from June 2022 to December 2022. Thus, the ICU stay can be 1–3 years before the EQ-5D valuation interview. The interviews for the Danish general population valuations were carried out between October 2018 and November 2019. The distributions of the EQ-5D-5L valuations from the patients and the general Danish population will be compared both graphically and numerically, as presented in Devlin *et al*.[1]

Composite time trade-off

For comparative purposes, this study follows the EQ-VT including cTTO, which was used to collect Danish EQ-5D-5L values.[23] The time trade-off (TTO) method of elicitation was developed for use in healthcare[32] and is most commonly used today when eliciting valuations for health states.[33] In conventional TTO, the value of a health state (considered better than dead) is evaluated by a series of adaptive choices between x years in full health and 10 years in poor health[33 34] (see figure 1). Through an iterative process, x varies until the patient is indifferent and then the health state is valued as x/10. However, this conventional approach is problematic when the health state is considered worse than dead. In these cases, lead time TTO is used.[25 33 35] Here the patient has to evaluate health states in a series of adaptive choices between x years in full health and a situation with 10 years in full health followed by 10 years in the considered health state (see figure 1). Again, x varies until the patient is indifferent and then the health state is valued (x–10)/10. cTTO is a compromise between the conventional TTO and lead time TTO, making it possible to avoid having to use different tasks to elicit preferences for health states better and worse than dead.[25 26]

EuroQol Valuation Technology

The EuroQol Valuation Technology (EQ-VT) has been used to generate EQ-5D-5L value sets in 24 countries to date (https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/). The most recent EQ-VT version (2.1) was used in the Danish population valuation study[23]; we will also use this version to elicit EQ-5D-5L health states from ICU patients.[26 33] A portable (EQ-PVT) version of EQ-VT will be used. The EQ-PVT is administered through a computer-assisted face-to-face interview. The interview will include six elements as presented in box 1. A visual aid is presented on the screen to illustrate the cTTO task for the patient[26] (figure 1). Contextual questions (see online supplemental appendix A) are included to investigate the heterogeneity in health state valuations.

Four changes to the standard protocol[26 33] in EQ-VT are needed: (1) inclusion of Mini-Version Montreal Cognitive Assessment (Mini-MoCA), (2) inclusion of 15 health states (explained in a following section), (3) inclusion of some contextual questions regarding the ICU stay, and

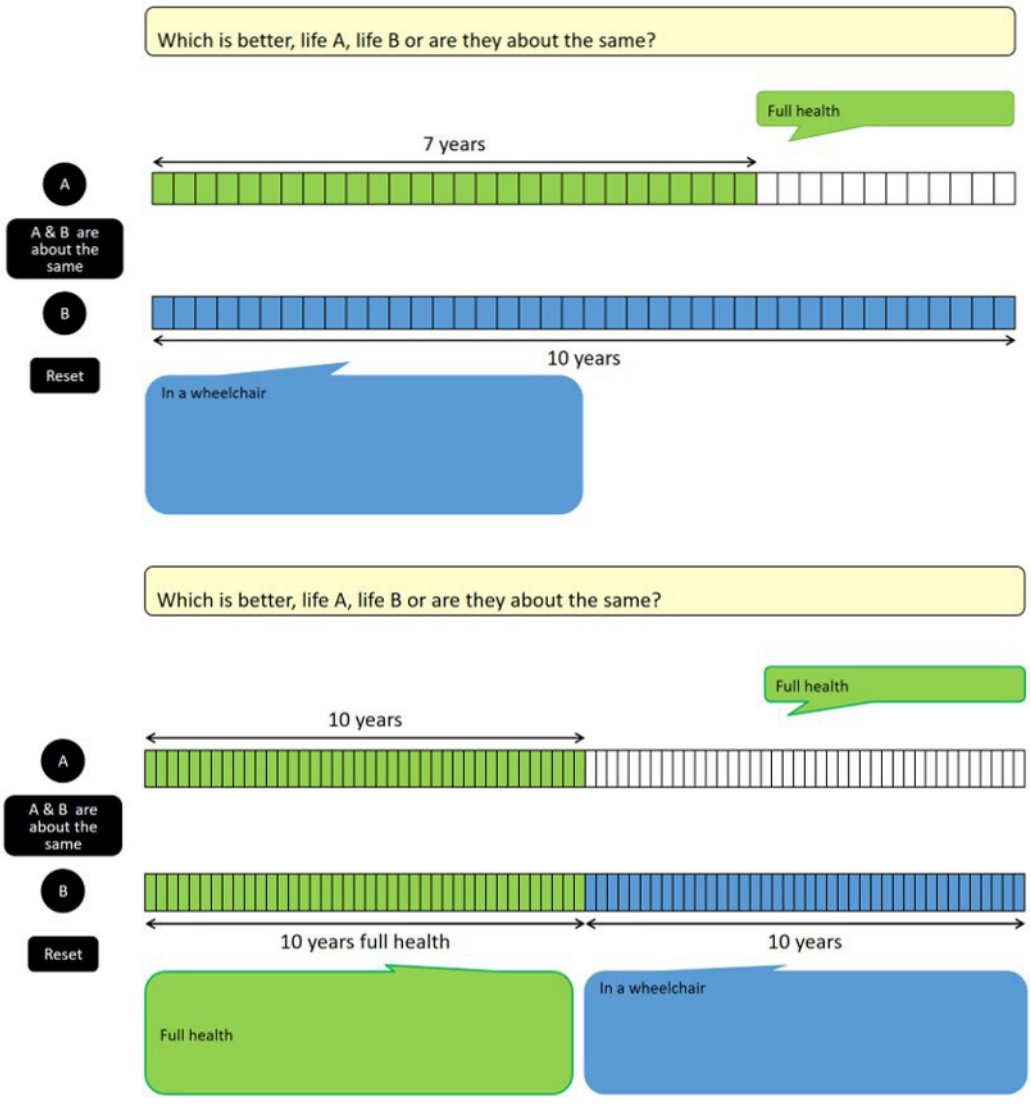

Figure 1 Visual aid of the composite TTO. 'Wheelchair example' of conventional TTO with a 10-year time frame and lead time TTO with a 20-year time frame. Conventional TTO when health states are assessed better than dead. Lead time TTO when health states are assessed worse than dead. Source: EQ-PVT.[37] TTO, time trade-off. EQ-PVT, portable version of the EuroQol Valuation Technology

(4) exclusion of the discrete choice experiment tasks to reduce respondent burden.

Most of the background and contextual questions were used in the EQ-5D-5L valuation study with the Danish general population, thus enabling comparisons between the patient and general population settings. The first three and last 10 questions in online supplemental appendix A have been developed for the current study to help interpret patients' responses and investigate heterogeneity in cTTO responses. These questions were tested in a pilot study with 10 persons. To avoid influencing the cTTO valuation, the questions are placed at the end of the interview. Two questions explore potential changes in the patient's reluctance to trade-off longevity for HRQoL: 'Would you have answered differently before the ICU stay? Would you have been willing to 'sacrifice' more/fewer years for quality of life before the ICU stay?' The last 10 questions ask for background information including age, number of children, the reason for ICU admission, and recovery time after the ICU stay.

In this context of interviewing surviving ICU patients, it is estimated that the interview will take 1.5 hours as more breaks and explanation than usual might be needed. If the patient is tired or feels unwell, the interview will be paused or stopped.

Health state blocks

The EQ-VT protocol recommends a sample size of a minimum of 1000 respondents, where each respondent values 10 health states resulting in 10 000 responses.[14 26] In the ICU setting, we expect to need a longer time horizon to include all patients in the study than in settings with the general population due to the patients likely being in poorer health. To optimise the number of responses within the plausible period for this patient group, we plan to operate with a sample size of 300 respondents each

Box 1 Elements of the EQ-5D-5L valuation interview in this study

Start interview
1. General welcome
   - Patient information read by the patient.
   - Informed consent signed by the patient.
2. Mini-MoCA[38 40]
3. Introduction
   - Self-reported health on the EQ-5D-5L descriptive system.
   - Self-reported health on the EQ-VAS.
4. Health state valuation using cTTO
   - Instructions and example of cTTO task +3 practice states (including the 'wheelchair example' and 'worse than dead task').
   - cTTO valuation of 15 EQ-5D-5L states.
   - cTTO debriefing/structural feedback (showing the patient which rank ordering of health states their responses result in).
   - cTTO feedback module (patient can then indicate disagreements with the rank ordering).
5. Background and contextual questions (see online supplemental appendix A).
6. General thank you and goodbye.

End interview

cTTO, composite time trade-off; EQ-5D-5L, 5-level EuroQol 5-dimensional questionnaire; EQ-VAS, EuroQol Visual Analogue Scale; Source, EQ-VT protocol version 2.1 with relevant changes; Mini-MoCA, Mini-Version Montreal Cognitive Assessment.[33]

valuing 15 health states, resulting in 4500 responses. The details of the standard EQ-VT protocol versus the EQ-VT protocol with 15 health states (developed in cooperation with EuroQol) are illustrated in table 1.

In the general EQ-VT protocol, health states are evaluated in 10 blocks of 10 health states. Blocks represent a randomised allocation of health states to minimise the burden on the individual respondent while ensuring that enough health states are valued to generate statistically robust preference estimates. To maximise the number of responses for each health state, we will operate with only 6 blocks of 15 health states (table 1). This approach is recommended by EuroQol and is being used to elicit the (not yet published) Australian EQ-5D-5L value set.[36] The reduction of blocks will increase the number of responses per health state and thereby minimise the role of noise, outliers and randomisation error. Even then, we will be operating with fewer responses per health state (ie, 50) than normal. Previous studies have used approximately 100 responses per health state.[14 34]

Table 1 Standard EQ-VT protocol versus EQ-VT protocol with 15 states

	Standard EQ-VT protocol	EQ-VT protocol with 15 states
Blocks	10	6
Health states in each block	10	15
No of respondents	1000	300
No of respondents per health state	100	50
No of responses	10 000	4500
Health states valued directly	86	86
Health states values modelled	(3125–86)=3039	3039

EQ-VT, EuroQol Valuation Technology.

Analysis and statistical modelling

The EQ-5D-5L describes 3125 possible health states (5^5). We estimate health state valuations for all health states by extrapolating the valuations that ICU patients have provided on 86 selected health states valued directly (table 1). These 86 health states are the standard health states used in valuation tasks.[1 14 33 34] A full valuation is produced by using econometric modelling to extrapolate from the valuations of the 86 health states to the full set of health states.[1] According to EQ-5D protocols, the modelling approach should be chosen according to the nature of the cTTO survey data.[26] Several regression techniques can be used, such as Tobit regression, censored least absolute deviation, two-part model and latent class models.[33] Censoring, heteroscedasticity, truncation and preference heterogeneity have been shown to appear in cTTO data.[33] Different approaches to handling these phenomena are described in the latest update of the EQ-5D-5L valuation protocol.[33] Model performance will be evaluated, through for instance goodness-of-fit, and based on this we will decide the most appropriate modelling approach.

Data quality and interviewer training

For the collected data to be approved by EuroQol's quality control (QC), each interviewer must conduct between 70 and 130 cTTO interviews; therefore, there will be a maximum of four interviewers for our 300-person sample.[37] These interviewers will have a bachelor's degree as a minimum. They will be trained following the EQ-VT training material and the EuroQol interviewer instructions document.[26] All interviewers will complete 5–10 test interviews, to familiarise themselves with the interview. Further, the interviewers will be certified in the use of Mini-MoCA.[38] The QC process has been shown to improve interviewer protocol compliance and data quality.[37] Evaluation of the collected interviews and interviewer compliance will be discussed at appropriate intervals (dependent on the quality of the data) with a EuroQol contact person. Interviews can be removed from the study if protocol standards are not fulfilled, and interviewers can be retrained or excluded. We will follow EuroQol's recommendations.[26]

Mini-Version Montreal Cognitive Assessment

Conducting interviews with patients is more demanding than conducting interviews with members of the general population.[12] Patients are likely to become tired during the interviews, and some may be unable to complete interviews due to the severity of their illness. Some patients will have impaired cognitive function at the time of the interview. At a 12-month follow-up assessment, around 24% of

all ICU patients were found to have cognitive function scores similar to those of patients with mild Alzheimer's disease.[39] Thus, we need an approach allowing us to exclude patients with impaired cognitive function.

We will use the Danish Mini-MoCA, which has been shown to be a valid and reliable cognitive screening tool for several patient groups.[38] The Mini-MoCA consists of four domains: attention (immediate recall of five words), executive functions (name words beginning with the letter F in 1 min), orientation (date and geographical orientation), and memory (recall the initial five words). Our interviewers will be trained and certified in the use of the Mini-MoCA. The certification will be an add-on to the interviewers' EQ-VT training and will be conducted through the online 1 hour Training & Certification module.[40] Patients scoring low on the test will be excluded.

Comparison of patient and public valuations

When comparing the patient-specific valuations to those of the general population, we need to assess the differences in personal characteristics between the general population and the ICU patients aside from the ICU stay. Comparisons of patient and general public valuations will be based on two types of analyses. First, we will compare the demographic characteristics and self-reported health status of the patients with those of the general population from the Danish valuation study, as the demographic characteristics can be underlying determinants of the values estimated.[23] From this we will construct a sample from the Danish valuation study[23] with characteristics similar to those of the ICU sample; from this constructed sample, we can compare the valuations between the two groups with similar characteristics. Second, we will assess the possibility of removing the imbalance in the number of observations between the sample of patients (around 300 observations) and the sample of representatives from the general population.[1] Thus, we will randomly include only half of the general population sample, model their valuations, keep the parameters and then repeat this (eg, 100 times) to obtain an average estimate of the parameter and a bandwidth.

Investigating the heterogeneity in preferences

To try to understand the heterogeneity in preferences, we will investigate various factors that might influence preferences for health states by pursuing the aforementioned research questions using the following strategies.

1. To investigate which factors might influence ICU patients' preferences, we will use various personal characteristics in a regression analysis to identify potential underlying determinants of the EQ-5D-5L values for the 86 health states valued directly. These include demographic characteristics (eg, age, gender, place of residence, immigrant status) and self-reported HRQoL (derived from E5-5D-5L responses). Further, duration (time since the ICU stay) can be used as a potential explanatory variable due to the variation in the time gap across respondents. The ICU stay can be 1–3 years before the EQ-5D valuation interview. This variation provides two opportunities: (1) to assess whether valuations are stable among ICU patients and (2) to assess whether respondents' valuations change over time in a manner that may imply adaptation. Lastly, we will include the background and contextual questions from the EQ-5D valuation interview, for example, the reason for the ICU stay, the importance of different dimensions of EQ-5D on quality of life, health status and prior experience of illness.
2. During the interview, we ask the patients whether their ICU stay has changed their reluctance to trade-off longevity for HRQoL. The question is: Would you have been willing to 'sacrifice' more/fewer years for improvements in quality of life before the ICU stay? This item can be used to qualitatively examine the patient's own view of their willingness to trade-off length of life and quality of life. This question can moreover be used to examine whether the 86 directly valued health states changes according to the respondents' answers. Those who respond that they are less/more willing to give up life-years after their ICU stay is expected to express higher/lower valuations for the particular health states.

Further, we can assess the trade-off between longevity and HRQoL by examining all extrapolated health states by investigating the ranking of health states based on the patient's respondents and the ranking based on the public's respondents. If the ranking of health states remains intact despite valuations being different, this would suggest that it is the value of life-years that has changed and not the preferences for specific health outcomes.

3. 'Health state reference dependency' is used to describe the situation where a respondent's valuations of health states are dependent on the respondent's own health.[18] Some evidence of reference dependency has been found by Jonker *et al*[18] (on DCE data). These authors found that respondents with impaired health lower than or equal to the health state level under evaluation expressed preferences that indicated 30% smaller health state decrements compared with respondents without health problems.[18] They also found that reference dependency does not bias QALY estimates. The experience of very bad health may change people's ideas about which type of problems they could cope with. A change in one health dimension may not only affect the valuation for that dimension but may also change the person's valuations for other health dimensions. This information about their current health state will be used to assess any observed changes in valuations, primarily on the dimensions where the patient gives a low score.

In our sample of ICU patients, we will investigate whether it is possible to define a new reference point for these former ICU patients. We hypothesise that larger valuation deviations will be seen for health dimensions

where the patient has gained experience during their illness. The reference point will be examined through the patients' responses to the EQ-5D-5L items about their own health. To investigate whether this reference point influences the health state valuations, we select health states that involve changes in the attributes where the patient performs poorly and see if these health states are assessed differently among these individuals than for other individuals. This is done in a regression analysis where we simultaneously control for other explanatory factors. The focus is on the 86 directly valued health states.

Patient and public involvement

Patients and the public were not involved in commenting on the study design or the writing of the manuscript. The questions have been piloted on some members of the general population.

DISCUSSION

We believe this to be the first EQ-5D-5L health state valuation study involving patients who have survived an ICU stay. A key strength of this study is that we can compare the estimated preferences to those of the general Danish population as we have access to the data of the newly published Danish value set generated from the general Danish population.[23] This study is primarily a methodological investigation. We will be generating a value set to answer methodological questions. The establishment of a patient value set that can be used for prioritisations will require a larger sample size in order to produce more robust valuation estimates.

Patients who are admitted to ICUs are a heterogeneous group concerning diagnoses. For example, patients' diagnoses and conditions include trauma, oncology disorders, respiratory failure, liver failure and septic shock. In addition, the severity of patients' conditions varies greatly (some may have been close to death, while others have had milder symptoms) and the length of patients' ICU stays differs. Some patients will have chronic quality of life impairments after the ICU stay, and some will not. However, ICU patients undergo similar experiences in terms of the sudden high risk of death (20.7% die within 30 days) and respiratory support (45.7%).[41 42] Thus, a strength of this study is that we are dealing with a broad array of health events that enables us to explore whether people who have experienced critical illness and intensive care express preferences for health states that differ from those of the general population.

An important modelling issue could limit the precision and identification of this study. As we only include 300 patients, we expect that the SD in our valuation study will be larger than a similar study that uses the 1000 respondents prescribed by the standard protocol for EQ-5D-5L valuations.[26 33] The smaller patient sample size also may lead to the number of spikes, gaps and clusters being larger for the patient population than for the general population. These undesirable features can diminish the sensitivity of the resulting health state valuations.[1] This will be addressed in the modelling analysis and through the QC process as described. Previous valuations of patient-based preferences have been based on around 280–330 patients.[12] Another modelling limitation arises as the patient-based and the public-based valuations use different elicitation methods. The Danish population valuations are based on a hybrid model of cTTO and DCE,[1 23] whereas we will only use cTTO interviews with patients to minimise the burden of the interview. An option to assess the potential model biases is to do a sensitivity analysis comparing just cTTO valuations from the Danish population with those of the patients.

Several issues related to the inclusion of patients are relevant to consider. First, the inclusion of patients depends on successful recruitment in the two RCTs—HOT-ICU and CLASSIC. If these two RCTs do not achieve sufficient patient numbers, we will include more RCTs from ICUs in Denmark. Second, when we include patients from ICUs, their valuations will not be elicited during their ICU stay as the patients would be too ill to participate. Therefore, we will only elicit valuations from ICU survivors.

Given the lag of 1–3 years from the ICU stay to the valuation interview, recall bias may impact responses when we ask patients about whether their preferences have changed. Recall bias is particularly an issue when we pose questions such as 'Would you have answered differently before the ICU stay? Would you have been willing to 'sacrifice' more/fewer years for quality of life before the ICU stay?' These questions will be used to support a discussion of possible explanations for differences in valuations. We will seek to provide evidence of a potential presence of recall bias by comparing responses provided with a lag of 3 years vs responses provided after only 1 year.

The COVID-19 pandemic may also bias the result as the public-based valuations were conducted before COVID-19 emerged while the patient-based valuations will be conducted during/after a COVID-19 upsurge. A recent UK study[43] indicated that COVID-19 may have had an immediate influence on the UK public-based valuations. The study does not, however, provide clear evidence of the policy relevance of such changes, nor does it address whether these changes are highly temporary or more long-lasting. It is likely that the impact is only temporary and that the ICU experience will outweigh the impact of the COVID-19 pandemic on preferences. Thus, we would argue that applying pre-COVID-19 valuations as the benchmark in our study is the more robust strategy. Further, we hypothesise that patients' preferences are more likely to be influenced by their personal health experiences than COVID-19, assuming they were not infected during the pandemic. We have included two questions to the background questions: 'Have you or a close family member had COVID-19 since your ICU stay?' And 'If yes, how serious was it?' Further studies are needed to understand the potential influence of COVID-19 in studies where pre-COVID-19 is assumed unchanged.

The study contributes to the existing literature by allowing comparison of the EQ-5D-5L valuations for patients with those of the Danish national sample, and it may also be possible to model the whole EQ-5D-5L value set for the patients. This would enable us to test the effect of using the patients' valuations in economic evaluations, bearing in mind the potentially larger SDs due to fewer respondents than in other valuation studies (300 vs 1000 respondents). Further, the study may help to identify any difficulties in recruiting patients to be respondents in a TTO interview and to get experience in handling complications during the interview due to a patient's potentially severe illness. This would contribute to the further development of the existing methodology and the EQ-VT protocol.

If the study finds no significant differences between the valuation of ICU patients and the general population, the existing practice of cost-utility analysis based on public-based valuations will be supported. With our focus on a patient group who has suffered a significant health event, this would indicate that a more general involvement of patient valuations in QALY calculations is unlikely to markedly influence the conclusions drawn from economic evaluations.

On the other hand, if the preferences of this patient group are different to public preferences, then the QALYs calculated—and hence the treatment decisions made for this patient group—may not reflect what the patients actually prefer. In that case, the current practice may lead to suboptimal allocation of resources. This finding would suggest a need for similar studies in other groups of patients experiencing serious health events.

ETHICS AND DISSEMINATION

Under Danish regulations, ethical approval is not usually required for studies of this type, and this has been confirmed by the institutional review board. Consent will be obtained for use of the data from the Danish national valuation study. Regarding our patient participants, oral consent will be obtained first over the telephone. Thereafter, written informed consent will be obtained from the patients in accordance with national regulations. The patients will be able to withdraw their consent at any time and will be informed about this both at the initial contact and at the face-to-face meeting. The interview will be conducted in the patient's room or in a quiet and closed room if at the hospital to make the situation as calm as possible. The patient has the right to have a relative attend the interview.

The results of the study will be published in peer-reviewed scientific journals and presented at relevant national and international conferences. The specific modelling algorithms will be publicly available for statistical software, such as Stata and R.

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Acknowledgements Innovation Fund Denmark and Helsefonden funded the research described in this paper. Danish Centre for Healthcare Improvements from Aalborg University provided access to data from the Danish EQ-5D-5L valuation study as well as invaluable input into interviewer training materials, translations of the interview materials, contribution of background questions and advice. Further, the paper has benefitted greatly from discussions with the EuroQol Group and the trial groups of HOT-ICU and CLASSIC. The EuroQol group provided the EQ-PVT.

Contributors CMBH and AP secured funding. CMBH and CG designed the study protocol. DG-H and CEJ recommended revisions. CMBH drafted the manuscript. All authors read and approved the final manuscript.

Funding Funded by Innovation Fund Denmark (4108-00011A) and Helsefonden (18-B-0159).

Disclaimer The funding does not involve the request for review of the findings prior to their release, and the authors bear the full responsibility for the analyses, the interpretations of results, and the conclusions drawn.

Competing interests The terms of this research project have been reviewed and approved by the Danish Centre for Social Science Research (VIVE) in accordance with its policy on objectivity and independence in research. VIVE is an independent national research centre working within the major welfare fields and affiliated with the Ministry of Economic Affairs and the Interior. CG is a member of the EuroQol Group.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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