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The construction and validation of the Severe Asthma Questionnaire (SAQ)

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Key Words:	asthma, outcome, Quality of Life

Dear Editor,

Thank you for giving us the opportunity to revise our paper. This has now been done and our replies to reviewers are shown below. We have copied and pasted the full reviewer comments, and these are shown in black. Our replies are shown in red.

We look forward to hearing from you in due course

Yours sincerely

Michael E. Hyland

Reviewer: 1

Comments to the Author
General Comments
This manuscript describes the quantitative validation of a new asthma-specific quality of life (QOL) measure, designed in accordance with FDA recommendations from 2009. Subsequent to previously published qualitative data, a 16-item questionnaire was designed and tested on patients with severe asthma.
The manuscript is well-written. Minor errors are apparent in the results section, and certain tables and figures would benefit from amendment or exclusion. A few additional points warrant mentioning in the discussion, especially that no distinction was made for participants on or off oral corticosteroids (OCS). Specific comments are outlined below.
Overall, this manuscript describes a new patient reported outcome measure (PROM) specific for severe asthma, considering elements that other PROMs do not. The SAQ is likely to be a valuable addition to the field.
We thank the reviewer for these positive remarks
Specific Comments
1. Abstract
a. The abstract is concise and reflects the manuscript.

2. Introduction
a. The introduction sets the appropriate context for the rest of the manuscript.

3. Method
a. Comprehensive methods section.
b. Grammatical error, page 4 line 32.

Thanks, the tense has been corrected

4. Results, Tables & Figures
a. Table 1 – for greater clarity please add gender and race demographics, as well as proportions on biologics and OCS if possible.
We agree and these have been added
b. Page 7, line 33 – seems to be referring to Table 2, not Table 3.
Yes, this has been corrected

c. Table 2 – good description in text and good representation of statistical significance in table.
d. Page 8, line 17 – it looks like the authors are referring to Table 3, not Table 2.
Thanks, this has been corrected
e. Table 4 is good.
f. Table 5 – if authors wish to include this table, they should explain the OCS dose is an "estimated annual cumulative dose" (consider inserting this as a title, in the style of Table 4).
We agree and have added the word estimated as suggested
g. Please explain why 6595mg OCS per year is a clinically relevant cut-off, as this is still not clear within the text.
The dose of 6595 OCS per year was chosen as this is nearer a prednisolone equivalent dose of 20mg/day. This allowed appropriate cut offs to allow meaningful statistical analysis but also cutoffs that were relevant to patients and clinicians.
h. Figure 1 is good.
i. Figure 2 does not include all of the questionnaires in the graph. Consider amending or removing.
Thanks for pointing this out- we considered this before submitting. The two questionnaires shown in Figure 2 use 7 point response scales, and so are comparable. Other questionnaires have different response scales have other response scales and are therefore not comparable. We also considered normalising the results, but this creates other problems as the AQLQ has a tighter (i.e., less varied) distribution compared to the SAQ. As the AQLQ is the main comparator for an asthma specific clinical trial, we wished to highlight the slight difference between these two scales.

5. Discussion
a. This section is well constructed.
b. As the SAQ was designed specifically in response to existing PROMs not considering OCS burden (Ref. 10), it is important to mention that no distinction was made for patients on or off OCS. This might be a limitation to the study, or it might suggest the SAQ is advantageous irrespective of OCS burden in severe asthma.
Thank you for helping us clarify this point – we address it now in the conclusions, i.e., the SAQ is validated in a severe asthma population with different patterns of treatment.
c. It is worth mentioning in the discussion that the better results seen for the 0.5-9.5mg OCS group (in Table 4) were not statistically significant, and "may simply be due to random error".
This was checked out to make sure and in fact there are significant differences. We have explored this further and presented data showing it is possible that the difference is due to the higher proportion of patients on biologics in that group.
d. Page 10, line 38 – "and 18% rated it [very difficult] for other family members." Consider amending sentence as shown.
Thanks, we have amended as suggested.
e. Page 12, line 41 "use of biologics… would not be expected to affect comparisons between outcome measures." But the use of biologics might reduce the need for oral steroids.
We have removed this comment. The referee is correct, but this raises numerous issues that this paper cannot address (see point c above). It is likely that there is a

complex relationship between biologics and OCS on quality of life that requires further investigation.

f. Under limitations, no comment made for level of literacy needed to complete questionnaires.

We have calculated the Smog reading score and have presented this in the introduction. The Flesch score and Flesch-Kincaid reading score may be more familiar to readers, but these have been criticised recently and the new recommendation is to use the Smog.

g. The study was done in the south west of the UK, which is not a diverse population. This should be specified as such within the limitations section without the implication that the study generalises to the UK population as a whole.

The UK severe asthma registry has published demographic data of patients with severe asthma.

We accept that the South west of UK is not a particularly ethnically diverse population and completely agree with the reviewer this should be stated within the limitations. However we feel the population is not dissimilar to the UK demographic data presented within the UK severe asthma registry. E.g.

In all the centres contributing data 91% of patients with severe asthma were white (100% in Belfast and 96% in Manchester).

However further validation in ethnically and culturally diverse populations is required.

6. References

a. The manuscript is appropriately referenced.

Reviewer: 2

Comments to the Author

The authors have produced a well written manuscript detailing the construction and validation of a novel PROM for severe asthma.

Major criticisms:

1. Please explain in the introduction why 2 components are required for this novel PROM, i.e. both the SAQ and SAQ Global.

Thanks for raising this important issue which is now explained and referenced in the introduction and the issue returned to with additional references in the discussion.

2. The demographics table would benefit by being expanded to show the data for each of the GINA steps.

We have expanded the demographic table as suggested separating GINA step 4 & 5 and including ethnicity and ICS dose (mean 1700mcg/day).

See table.

3. Why have GINA 2 and 3 patients been included in the analysis when they are outside the ERS/ATS definition of severe asthma?

We thank the reviewers for pointing this out.

These patients were identified through our Emergency department follow up service (rather than the severe asthma clinic) and although were all in a stable state (>4 weeks post exacerbation) they were at higher risk due to previous exacerbations, still symptomatic and therefore deemed eligible for enrolment into the study.

The one patient at GINA step 2 was seen as follow up for a previous Emergency Department visit and although did not meeting the criteria for severe asthma was at higher risk and enrolled in the study erroneously. As the study was based on an intention to treat the data has been included although we have now stated this clearly within the text.

The GINA 2016 asthma guidelines state Step 4 asthma treatment is defined as requiring Medium / high dose ICS/LABA.

Medium dose ICS = 500-1000mcg/day BDP equivalent

High dose > 1000mcg/day BDP equivalent

On further reviewing these patients they meet the criteria for classification as GINA step 4.

Of the 10 patients previously classified as GINA step 3:

3 patients were on ICS > 1000mcg /day BDP equivalent

5 patients were on ICS 1000mcg/day BDP equivalent

2 patients were on ICS 800mcg/day BDP equivalent

All were receiving an ICS / LABA combination.

Therefore we thank the reviewers for highlighting this discrepancy and we have reclassified the patients into the appropriate GINA step 4 classification.

4. Please explain mean prednisolone dose ranges? Why not 10-20 and greater than 20?

These dose ranges were selected on a statistical basis to achieve approximately equal group sizes. This has now been stated in the results section.

5. Please explain the cumulative OCS ranges? 1120mg/year is equivalent to 40mg od for 7 days on 4 occasions and I disagree that this is more clinically relevant than 840mg for instance (30mg od for 7 days on 4 occasions).

These are estimated cumulative OCS doses and as such likely to be an underestimate of the true overall steroid burden.

In our experience patients with severe asthma who exacerbate will frequently have at least 1 week of high dose prednisolone but often have longer courses of OCS than 1 week, not infrequently requiring a steroid taper.

We completely agree that a cumulative OCS dose of > 840mg is clinically relevant but for pragmatic reasons we defined the estimated OCS burden of 1 exacerbation as prednisolone 40mg OD for 7 days. This figure was chosen as the British Thoracic Society 2016 asthma guidelines advise prednisolone 40-50mg/day for at least 5 days or until recovery.

The GINA 2016 guidelines advise:

Adults - prednisolone 1mg/kg/day up to 50mg, usually for 5–7 days.

We have added this to the text

6. Please add to the discussion an explanation as to why the 0.5-9.5mg OCS group have a better ACT and SAQ than the other groups. It may be due to random error, or it may be that low dose OCS improves asthma, which, after all is why it is used clinically. Surely this will need to be reviewed in larger numbers to see if this is a true finding,

It is actually statistically significant for some but not all outcome measures. We have explored this further and presented data showing it is possible that the difference is due to the higher proportion of patients on biologics in that group.

In addition, if you have not already done so, please compose a short sentence of 120 characters or less summarising the most important findings, or message, of your study. This will be published alongside the abstract of your article and will allow the ERS to generate interest in your study via its official publications Twitter feed (@ERSpublications).
This was done in the original version and shown on the front page.

The construction and validation of the Severe Asthma Questionnaire (SAQ).

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Author contributions

All four authors contributed to the design of the study and all four authors contributed to the writing of the paper. MH wrote the first draft and was responsible for the analysis. MM and RJ were responsible for recruitment and data collection. JL collected the data and contributed to the analysis.

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Take Home Message

This paper describes the validation process for a new severe asthma specific quality of life questionnaire, the SAQ.

Running title: Severe asthma quality of life assessment.

Abstract

Background

The USA's Food and Drug Administration's procedure for scale validation requires a documented stepwise process of qualitative and quantitative data. The aim of this paper is to provide the final quantitative validating data.

Methods

The severe asthma questionnaire (SAQ), asthma control test (ACT), MiniAQLQ, and EQ-5D-5L were completed by 160 patients attending a severe asthma clinic; 51 patients completed the SAQ on two occasions for test-retest reliability analysis. The SAQ produces two scores, an SAQ score based on the average of 16 items and a SAQ-global score from a single 100-point global quality of life scale.

Results

Construct validity was demonstrated through factor analysis of the 16 items, convergent validity by correlations of > 0.6 between the SAQ, SAQ-global and other questionnaires, and discriminant validity by the ability of the SAQ and SAQ-global to distinguish between different treatment levels. Test-retest reliability (intra-class correlation) was 0.93 for the SAQ and 0.93 for the SAQ-global, and the alpha coefficient for the SAQ was 0.93.

Conclusions

The SAQ was developed using recommended qualitative and quantitative procedures for scale development, and can be used to gain insight into patients' perceptions of the impact of severe asthma and its treatment on their lives.

Keywords: Asthma; Outcome; Quality of Life.

Introduction

Patients with severe and difficult-to-treat asthma comprise a small proportion (5-10%) of all asthmatic patients, yet are responsible for a disproportionate degree of asthma morbidity and costs [1,2]. Quality of life assessment forms an essential part of asthma assessment as measures such as respiratory symptoms and lung function may not convey the true limitations caused by the disease from the patient's perspective [3]. Compared to mild and moderate asthma, patients with severe asthma have additional quality of life deficits caused by multiple and more severe exacerbations that disrupt the lives of patients and their relatives, comorbidities, and higher treatment burden, particularly oral corticosteroids, [4].

The US Food and Drug Administration (FDA) published recommendations for validating Patient Reported Outcome Measures (PROMs) in 2009 [5]. The FDA recommends a stepwise process of validation where *firstly* content validity is established by documented qualitative research and *secondly* construct and other validity is established through quantitative methods.

The three most commonly used asthma specific health related quality of life (HRQoL) scales [6, 7, 8] were published prior to the FDA's 2009 guidelines and include symptom items that are perceived negatively in this context by patients [9]. Additionally, these and other published asthma scales fail to assess quality of life deficits specific to severe asthma [10]. Thus, although existing scales are valid in terms of earlier definitions of validity [11, 12] or for mild and moderate asthma, they are not valid in terms of the FDA's 2009 guidelines when used in people with severe asthma.

The qualitative stage of the development and content validation of the severe asthma questionnaire (SAQ) has been reported in two studies [10,13]. The first study [10] showed that in addition to deficits experienced in mild and moderate asthma, those with severe asthma had additional problems in their lives primarily caused by two factors. First, the side effects of medication produced a variety of problems including mood changes, changes in self-perception, problems with eating, sleep disturbance, and appearance. Second, exacerbations (in particular those leading to hospitalisation) created problems for the patient and the wider family.

Using our findings from the first study we drafted a severe asthma specific questionnaire, and subsequently conducted four focus groups in which patients with severe asthma provided iterative changes to the design and content of the draft questionnaire [13]. The aim of this second phase was to ensure that the questionnaire was able to correctly capture the kind of information patients felt important in relation to their quality of life. Patients defined the response scale, combined two items, split one item to assess different impacts on family lives, advised on recall period and optimised the wording of individual items. In addition, patients expressed a desire to provide an overall assessment of their quality of life (see the online supplement, Figure E1).

The SAQ comprises 16 questions about different aspects of life and a global question that assesses their quality of life overall. The SMOG grade [14] for the SAQ is 5.9, indicating suitability for a reading age of at least 11-12 years. The unweighted aggregation of the 16 questions produces a score similar in methodology with other quality of life questionnaires. The additional global question is used for two

reasons. First, patients express a strong preference for providing an overall score in contrast to those requiring a differentiation between different aspects of life. The second reason is psychological. Patients make judgements, including judgements about their lives, using either one or a combination of two cognitive processes, called System 1 and System 2. System 1 judgements are fast, automatic and the process unavailable to consciousness. System 2 judgements are slow, deliberative, and people can introspect the process [15]. A patient's response to a question in clinic 'how are you?' will be influenced primarily by a System 1 judgement. The use of two types of measure, the SAQ score based on the 16 items and the SAQ global score provides a way of capturing these different kinds of judgement [16]. Single item scales are less preferred in clinical trials because the use of multiple items reduces error variance.

The aim of this study was to provide the final stage of validation required by the FDA, namely a quantitative study that establishes construct and other types of validity.

Method

Participants

Patients diagnosed with severe asthma as defined by the international consensus statement from the European Respiratory and American Thoracic Societies [1] aged ≥16 years of age who attended the Plymouth severe asthma service were invited to participate. Those with significant other conditions contributing to their respiratory symptoms, e.g. lung cancer, heart failure or severe COPD were excluded.

Questionnaires

Severe Asthma Questionnaire (SAQ) comprises 16 items, with response options on a 7-point scale averaged to produce the SAQ score (scores 1 – 7) and a 100-point Borg-type scale [17] producing the SAQ-global score (scores 0 – 100). Quantifiers are indicated against all seven of the SAQ response options. A Borg scale is a category rating scale with quantifiers at either end and additional, empirically placed quantifiers along the categories of the scale. The SAQ-global was adapted from an existing global quality of life scale [18] see www.saq.org.uk.

Mini Asthma Quality of Life Questionnaire (MiniAQLQ) [7] comprises 15 items with response options on a 7-point scale with responses averaged (scores 1-7).

Asthma Control Test (ACT) comprises five symptom and medication items (5 response options per item) totalled to produce an asthma control score. [19].

EQ-5D-5L comprises five quality of life items (5 response options per item) which were averaged to produce an EQ-5D-5L score and the *EQ5D-VAS*. A 100-point visual analogue scale (scores 1 – 100) [20].

Criteria for missing data are shown in the online supplement.

Clinic data

Clinic data collected were: spirometry (FEV1), prednisolone dose (mg/day), number of severe exacerbations in the last 12 months requiring systemic steroids, Global Initiative for Asthma (GINA) severity, BMI, estimated cumulative oral corticosteroid

(OCS) dose per year. This was calculated by multiplying the participant's maintenance steroid dose by 365 days, and adding an estimate of OCS use per exacerbation in the previous 12 months. Based on British Thoracic Society and GINA guidance one exacerbation was judged to comprise prednisolone 40mg/day multiplied by 7 days which equates to 280mg of prednisolone per exacerbation [21,22].

Procedure

Patients were recruited to the validation study or the reliability study or both studies. Questionnaires were completed either at home (postal return of questionnaire) or in clinic. Participants' data were included in the analysis of test re-test reliability if their ACT scores did not change by the Minimum Clinically Important Difference (MCID) of 3 points or more and they reported stable asthma (see online supplement, Figure E2).

Analysis

Analysis was on an intention to treat basis (see online supplement, Figure E2). Convergent validity between questionnaires was established using Pearson correlations. Groups of patients were identified by (a) level of maintenance dose of OCS (mg/day) and (b) estimated cumulative OCS dose per year. Differences between groups (discriminant validity) were tested by one-way analysis of variance (ANOVA) and where significant followed by Least Significant Difference (LSD) post hoc tests. Construct validity was tested by exploratory factor analysis using principal axis factoring following recommended practice [23, 24]. Evidence that the items could be aggregated into a single scale score was tested by examining whether the

scree test indicated a unifactorial solution and whether items loaded significantly (> 0.3) on the first factor. Test-retest reliability was calculated by intra-class correlations. Internal consistency was calculated by Cronbach's alpha coefficient. All analysis was conducted using IBM SPSS statistics 24.

Ethical approval

The study was approved by the Plymouth Hospitals NHS Trust and REC/HRA, ethical approval number 16/NE/0188, IRAS ID: 207601. All patients provided informed written consent.

Results

Questionnaire completion and return.

For the validation study 260 participants were invited to participate, 20 declined to participate, 54 failed to return questionnaires by post, and 26 patients failed to attend their clinic appointment and provide written informed consent leaving 160 participants. For the test-retest reliability study 115 patients were invited to participate, 10 declined. Of the 105 who consented for the test-retest reliability study, returned questionnaires were received from 67 patients, and 16 patients were excluded because their ACT score had changed by 3 points or more leaving 51 participants (37 female). (See online supplement, Figure E2). One patient at GINA step 2 was recruited although they did not meet the criteria for severe asthma they were at higher risk and enrolled in the study in error. Their data has been included in

the analysis as this studied used intention to treat criteria. Participant demographics are displayed in Table 1.

Of the 160 patients who participated in the validation study, completed questionnaires were as follows: SAQ (154/96% completed), MiniAQLQ (146/91% completed), ACT (159/99% completed). One hundred participants were asked to complete the EQ-5D-5L (96/96% completed).

Table 2 shows the correlations between the different questionnaires. All correlations were above 0.60, showing convergence between the different questionnaires. In addition, the correlations between all questionnaires, BMI and FEV1 percent predicted are also shown.

Table 3 shows the mean, range, and standard deviation of responses to the 16 items of the SAQ. Absence of floor or ceiling effects is indicated by no SAQ item having a standard deviation less than one point away from an end point. In addition, for all items participants used the full range of response options with some using every option between 1 and some 7 for all items (see Table E1 in the online supplement). These results show that no item should be rejected on the basis of poor distribution. The SAQ scores ranged from 5 (extremely bad quality of life) to 100 (perfect quality of life) (see Table E3 in the online supplement).

To test whether it is valid to aggregate the 16 items into a single scale score, exploratory factor analysis of the SAQ revealed a one factor solution using the scree

test (the first four eigenvalues were 9.91, 1.11, 0.92, 0.72,) accounting for 60% of the variance. The factor scores are shown in Table 3. All factor scores are above 0.6 showing that despite difference in content all items were related to the same latent variable. Cronach's alpha coefficient was 0.96. Test-retest reliability as measured by intra-class correlation was 0.93 (CI 0.87-0.96) for the SAQ and 0.93 (CI 0.86-0.96) for the SAQ-global, showing that the SAQ is a reliable scale. Test-retest reliability was also calculated individually for each item of the SAQ (see Table E3 in the online supplement).

Table 4 shows the mean and standard deviation score values for each of the six scales as a function of four groups of patients: no maintenance prednisolone, 1-9mg per day, 10 mg per day, and >10mg per day (ranges were selected to achieve groups of approximately equal size). All scales were significantly different across the four groups $p<0.001$, showing that the SAQ can discriminate between groups that are theoretically predicted to be different based on asthma severity. To compare the discrimination of different questionnaires between the 10mg/day and >10mg/day groups as a function of maintenance dose, we conducted LSD tests. Significant differences were found for the SAQ score (p =0.01), SAQ-global score (p=0.01) and EQ5D-VAS score (p=0.02), but not the MiniAQLQ score (p=0.13) nor the ACT score (p=0.34) nor EQ-5D-5L score (p=0.23). With regard to other paired comparisons, there is pattern of poorer outcome with increasing dose of OCS except for the comparison between those on no maintenance OCS versus those on between 1 – 9mg. For these comparisons (using LSD tests), the 1 – 9mg dose had better quality of life than the no maintenance dose for the MiniAQLQ (p=0.008), the ACT (p=0.001), the SAQ (p = 0.017) but not the SAQ-global (p=0.19), the EQ-5D-5L

(p=0.2), or the EQ5D-VAS (p=0.4). Because the 1 – 9mg dose group had better quality of life than the no maintenance dose group, we examined possible differences in biologic prescription between the four groups. In the zero dose group, 17/101 (17%) were on biologics whereas the figures for the other three groups were 1 – 9mg = 9/17 (53%), 10mg = 6/20 (30%), > 10mg = 6/22 (27%). Figure 1 provides a visual comparison of the SAQ and MiniAQLQ as a function of maintenance prednisolone dose.

Participants were allocated to estimated annual cumulative OCS dose groups: (a) 0 – 1119mg/year, (b) those on 1120-1460mg/year, (c) those on 1461-3650mg/year, (d) those on 3651-6595mg/year and (e) >6595mg/year. These doses were chosen to be clinically relevant, e.g. 1120mg/year ≈ 4 courses of OCS, 3650mg/year ≈ 10mg/day prednisolone, > 6595 ≈ 20mg/day prednisolone. Table 5 shows the mean scores for these five groups for each of the six scales. Figure 2 provides a comparison of the SAQ and MiniAQLQ mean scores at different doses of prednisolone.

One-way ANOVA showed that there was a significant difference (p<0.001) between the five estimated cumulative OCS dose groups for all questionnaires. In order to carry out post hoc tests that are equivalent to those of Table 4, we combined the two groups with the highest burden, namely those on 3651-6595mg/year and those on >6595 mg/year. ANOVA was repeated on the four groups (all questionnaires were significant at p<0.001). Significant differences were found between those on 1461-3650mg/year, and >3650 mg/year for the SAQ score (p>0.001), MiniAQLQ score (p>0.01), ACT total (p = 0.004), EQ-5D-5L score (p=0.003) and the SAQ-global score (p=0.006) and the EQ5D-VAS (p=0.04).

Discussion

The FDA's guidance for valid questionnaire construction [5] requires documentation of a qualitative stage of research followed by a quantitative stage. The SAQ was developed on the basis of qualitative research reported elsewhere [10, 13]. In this paper we provide details of the quantitative stage.

People with severe asthma experience difficulty in a number of different domains of life experience, some of which are not experienced by those with mild and moderate asthma. For example, 28% felt that irritability, a side effect of OCS, made life either very difficult or very, very difficult, and 27% experienced this level of difficulty with food. Thirty nine percent reported that 'problems at night' made life at least very difficult, where sleep disturbance can be caused either by asthma symptoms (which cause waking) or the side effects of OCS (which cause sleep difficulty getting to sleep, waking and additional problems during the night). Two family items are included in the SAQ as a result of the earlier qualitative research [13]. Twenty percent of patients rated their family lives as at least very difficult for themselves, and 18% rated it at least very difficult for other family members, confirming the earlier qualitative research that severe asthma impacts family life not only for the patient but also the patient's family. These descriptive results show that people with severe asthma can experience non-trivial disutility in domains of experience which are not included in questionnaires designed for mild and moderate asthma, with particularly high disutility recorded for 'the way I look', 'getting tired' and the two items assessing different worries about medication.

Although some people with severe asthma experience very poor quality of life, this is not a universal experience. For example, although 32% of people in this study felt they had moderately bad quality of life or worse, 24% felt they had good quality of life or better. Although some of this difference can be explained by severity and treatment differences (those with greater OCS burden report poorer quality of life) the relationship between severity, treatment and quality of life is complex.

In addition to providing descriptive data on people with severe asthma, the data provide construct validity for the SAQ. Statistical analysis showed that all 16 items could be aggregated into a single score and that no item should be rejected on purely statistical groups. The intra-class test-retest reliability of the SAQ and SAQ-global of 0.93 compares well with other questionnaires e.g. the MiniAQLQ of 0.83 [7]. The SAQ score and the SAQ-global score correlate with other asthma and generic scales thereby providing convergent validity. The SAQ score discriminates between groups of patients defined by maintenance prednisolone dose and defined by estimated cumulative OCS burden per year, thereby providing discriminant validity. There is a trend for the SAQ to demonstrate greater QoL impairment with increasing OCS burden compared to the MiniAQLQ but the study is underpowered to make statistical comparisons between scales.

All outcome measures showed a trend towards poorer quality of life with greater doses of OCS, except for the comparison between those on no prednisolone versus those prescribed between 1 and 9mg per day. We do not know why the 1 – 9mg group had better quality of life than those without a maintenance dose, but it may be due to the higher use of biologics in the 1 – 9mg group. Further studies are needed

to clarify the complex relationship between biologics and OCS on quality of life versus asthma symptoms [25].

The SAQ differs from other asthma-specific scales in that it includes a single item 100-point scale of global quality of life, the SAQ-global, which is included due to patient request. In this respect the SAQ is similar to the EQ5D where there is also a single item 100-point scale, the EQ5D-VAS. The SAQ-global is a 0-100 Borg type scale adapted from another scale [18], and research shows the use of additional quantifiers is more reliable than the format used in the EQ5D-VAS [15] where only the end points have quantifiers. With the exception of the EQ5D and EQ5D-VAS, all questionnaires show weak to moderate correlations with lung function indicating that lung function plays a modest causal effect on these measures. The absence of a significant correlation for the EQ5D and EQ5D-VAS suggests that these two measures may not be valid for assessing the quality of life of severe asthma.

Multiple item scales often have better reliability than single item scales for statistical reasons. Consistent with other research showing Borg scales to be more reliable than visual analogue scales [18], our data show that the SAQ-global is highly reliable and as reliable as the SAQ score. The SAQ-global also correlates well with other scales. Comparison between the EQ5D and EQ5D-VAS suggests that the EQ5D-VAS measures a broader concept than the EQ5D [16], and the same difference may apply to the SAQ score and SAQ-global. Additionally, response to these two different parts of the SAQ may reflect different cognitive processes – a fast automatic process for the SAQ-global and a slow deliberate process for the SAQ score [15]. Our study shows that ratings of ‘Good quality of life’ on the SAQ-global (i.e., those in the 70-79

range) equates to ‘makes my life slightly difficult’ (i.e. a mean score of 4.8 on the SAQ – see Table E3 in the online supplement), showing that the way a question is asked affects the patient’s response. Both types of measure can be useful, but it is likely that the SAQ-global provides a value more consistent with patients’ immediate response when clinicians ask about their asthma.

Limitations

The estimated cumulative OCS dose might be underestimate of OCS burden as patients with severe asthma may often require a longer course of OCS for an exacerbation than the 7 days used in our calculation. Use of biologics were not considered in this analysis and may affect quality of life assessments. The study was carried out in the South West of the UK, and although the study population is not dissimilar to the UK demographic data presented within the UK severe asthma registry [26], the population was predominantly Caucasian and further validation in ethnically and culturally diverse populations is required. The literacy level required to use the SAQ is at least age 11-12 years old reading level, but this is consistent with current literacy requirements for patient communication [27]. The 15-item MiniAQLQ rather than the 32-item AQLQ was used as a comparison scale to reduce questionnaire fatigue and because the MiniAQLQ is similar in length the SAQ. Nine patients participating in this study also participated in an earlier qualitative work [13].

.The SAQ is structured so that the global measure appears after the 16 contest specific items, and this order of presentation may have an effect. Research shows that prior exposure to a negative event (i.e., asking patients about difficulty in different contexts), will lead to a more positive subsequent judgement [28,29].

Further research is needed to explore how contextual factors, including the order of presentation of different questions influences quality of life judgements.

Conclusions

The SAQ was designed to detect the impact of both asthma symptoms and treatment on quality of life and has been shown to be content valid in earlier studies [10, 13]. This paper confirms the relevance of items based on the earlier studies, establishes the construct validity of the scale and shows it to be a reliable in a group of patients with severe asthma with different types of treatment. These data complete the validation procedures required by the FDA. Longitudinal studies are required to provide further information about the scale, for example, to establish sensitivity to change and the minimally clinically important difference in people with severe asthma. The SAQ is available for use in the British English version reported here and is available from the authors or online (www.saq.org.uk). Translations in other languages are required. In addition to providing a scale that is fit for purpose [10] for assessing health related quality of life in clinical trials, the SAQ can also be used in clinical practice to alert clinicians to the problems experienced by patients, and to gain an initial insight into the patients' own perceptions of the impact of illness and its treatment on their lives.

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Table 1.
Demographic information for all patients, those at GINA step 4 and step 5 of treatment.

	All (N=160)*	GINA Step 4 (N=100)	GINA Step 5 (N=59)
Female (%)	107 (66)	67 (67)	40 (67)
Age (range)	51 (16-78)	49 (16-74)	55 (25-78)
FEV1 (Litres) (range)	2.0 (0.7 - 4.4)	2.2 (0.72-4.3)	1.8 (0.7-3.6)
FEV1 (% predicted) (range)	72 (28 - 137)	75 (28-137)	65 (34-107)
Caucasian (%)	98	-	-
BMI (range)	31.8 (18.2-58.3)	31.0 (19.0 -58.3)	33.3 (20.7-57.9)
Median ICS dose (BDP equivalent mcg/d) (range)	1600 (400-4000)	1600 (800-4000)	2000 (1000-4000)
Number on Biologics			
Omalizumab	34 (21%)		
Mepolizumab	4 (3%)		

*One patient at GINA step 2 was included erroneously but included in the intention to treat analysis, see results section

Table 2. Pearsons' correlations between all six scales, BMI and FEV1 percent predicted (n)

	SAQ-score	MiniAQLQ-score	ACT-total	EQ-5D-5L score	EQ5D-VAS	SAQ global score
MiniAQLQ-score	0.76*** (140)	-	-	-	-	-
ACT-total	0.68*** (154)	0.84*** (145)	-	-	-	-
EQ-5D-5L score	-0.76*** (97)	-0.72*** (99)	-0.67*** (100)	-	-	-
EQ5D- VAS	0.71*** (96)	0.76*** (98)	0.66*** (99)	-0.79*** (98)	-	-
SAQ global scale	0.72*** (158)	0.71*** (140)	0.68*** (154)	-0.71*** (97)	0.76*** (97)	-
BMI	-0.31*** (154)	-0.25** (146)	-0.25** (159)	0.44*** (100)	-0.24* (100)	-0.22** (154)
FEV1 percent predicted	0.27** (154)	0.30*** (146)	0.24** (159)	-0.13 (100)	0.16 (100)	0.26** (154)

*p<0.05, **p<0.01, ***p<0.001

Table 3.

Mean, Standard Deviation, factor loadings, and the percentage of participants responding 'very difficult' or 'very, very difficult' to each of the 16 items of the Severe Asthma Questionnaire

Item	Mean*	Standard Deviation	Percentage of patients responding 'very difficult' or 'very, very difficult'	Factor loading
1. My social life. For example: visiting friends, walking with friends, talking with friends, going to bars/restaurants, and parties.	4.11	1.94	25.2%	0.88
2. My personal life. For example: washing, dressing, looking after myself, love life.	4.98	1.98	15.0%	0.81
3. My leisure activities. For example: walking for pleasure, sports, exercise, travelling, taking vacations.	3.54	1.95	37.5%	0.84
4. My jobs around the house. For example: housework, shopping, home maintenance, gardening.	3.96	1.92	27.2%	0.88
5. My work or education. For example, missing days, can't do all I want to do.	4.78	2.64	25.7%	0.6
6. My family life – how it affects me. For example: caring for children, family responsibilities	4.59	2	19.6%	0.87
7. My family life – how it affects others. For example: others taking time off work, problems with childcare, family members becoming upset.	4.74	2.1	18.3%	0.82
8. Depression. For example, feeling sad, fed up, blue.	4.05	1.98	29.0%	0.81
9. Irritable. For example, snap at people, get angrier than I should.	4.06	1.99	27.8%	0.77
10. Anxiety in general. For example, worry about things, always on edge.	4.03	2.1	29.7%	0.75

11. Worry that asthma may get worse. For example, medicines no longer help, more frequent attacks.	3.7	2.04	39.2%	0.71
12. Worry about long term side effects of medicines. For example, worry about cataracts, diabetes, bone fracture.	3.92	2.12	33.8%	0.66
13. Getting tired. For example, feeling tired for no reason, waking in the morning feeling tired.	3.16	1.9	43.3%	0.79
14. Problems at night. For example, difficulty going to sleep, being woken very easily, waking often at night.	3.5	1.99	39.2%	0.79
15. The way I look. For example, my weight, my skin bruises easily, using medicines in public, other people judging me	3.65	2.17	39.9%	0.68
16. Problems with food. For example, I find I get very hungry, I just can't stop eating, stomach problems (e.g., pain, bloating, etc.)	4.27	2.07	26.8%	0.67

* Interpretation of mean: In relation to quality of life, 1 = very, very difficult (worst possible); 2 = very difficult; 3 = difficult; 4 = moderately difficult; 5 = slightly difficult; 6 = very slightly difficult (just noticeable); 7 = no problem.

Table 4.

Mean, confidence intervals and *n-values* questionnaire scores and *n* at different levels of prednisolone dose

	Maintenance prednisolone dose ranges (mg/day)			
	0	1-9	10	>10
SAQ-score	**4.23** 3.93-4.54 *99*	**5.18** 4.55-5.81 *16*	**3.67** 2.96-4.40 *18*	**2.45** 1.90-3.00 *21*
MiniAQLQ-score	**4.20** 3.90-4.49 *92*	**5.21** 4.54-5.89 *16*	**3.57** 2.82-4.31 *18*	**2.89** 2.24-3.52 *20*
ACT-total	**14.36** 13.28-15.43 *101*	**19.63** 16.48-22.77 *16*	**12.00** 9.31-14.69 *20*	**10.36** 7.94-12.78 *22*
EQ-5D-5L score	**2.01** 1.79-2.23 *60*	**1.69** 1.24-2.14 *15*	**2.69** 2.14-3.23 *13*	**3.11** 2.48-3.75 *12*
EQ-5D-VAS	**65.40** 59.67-71.13 *60*	**70.47** 62.46-78.47 *15*	**55.77** 45.37-66.15 *13*	**35.67** 17.07-54.26 *12*
SAQ-global score	**58.92** 55.18-63.50 *97*	**66.38** 59.68-75.26 *17*	**51** 41.44-60.56 *20*	**34.05** 22.88-45.21 *21*

Note: a lower score for the SAQ-score, MiniAQLQ, ACT total, EQ5D-VAS and SAQ-Global score indicates low quality of life/health. A high score for the EQ-5D-5L score indicates poor health.

Table 5.

Mean, confidence intervals and *n-values* questionnaire scores and *n* at different doses of estimated cumulative OCS .

	Estimated annual cumulative dose (mg/year)				
	0-1119	1120-1460	1461-3650	3651-6595	>6595
SAQ-score	**4.52** 4.18- 4.85 *77*	**4.20** 3.49-4.91 *21*	**4.29** 3.56-5.02 *20*	**3.03** 2.52-3.55 *21*	**2.29** 1.60-2.99 *15*
MiniAQLQ-score	**4.45** 4.13-4.76 *71*	**4.32** 3.60-5.03 *22*	**4.33** 3.48-5.17 *18*	**3.24** 2.63-3.85 *20*	**2.65** 1.99-3.10 *15*
ACT-total	**15.19** 13.99-16.39 *79*	**16.14** 13.35-18.94 *21*	**14.62** 11.27-17.97 *21*	**11.14** 8.87-13.40 *22*	**8.81** 6.84 -10.79 *16*
EQ-5D-5L score	**1.89** 1.64-2.15 *46*	**2.02** 1.59-2.46 *17*	**2.03** 1.49-2.57 *13*	**2.67** 2.17-3.17 *15*	**3.40** 2.81-3.99 *9*
EQ5D-VAS	**66.85** 60.33-73.38 *48*	**71.67** 63.38-79.95 *15*	**60.15** 47.34-72.97 *13*	**57.67** 48.86-66.48 *15*	**22.56** 7.97-37.14 *9*
SAQ-global score	**61.45** 56.90-66.01 *75*	**62.76** 54.15-71.37 *21*	**54.52** 44.37-64.67 *21*	**47.95** 38.78-57.12 *22*	**25.67** 15.64-35.70 *15*

Note: a lower score for the SAQ, MiniAQLQ, ACT total, EQ5D-VAS and SAQ-Global score indicates low quality of life/health. A high score for the EQ-5D-5L score indicates poor health.

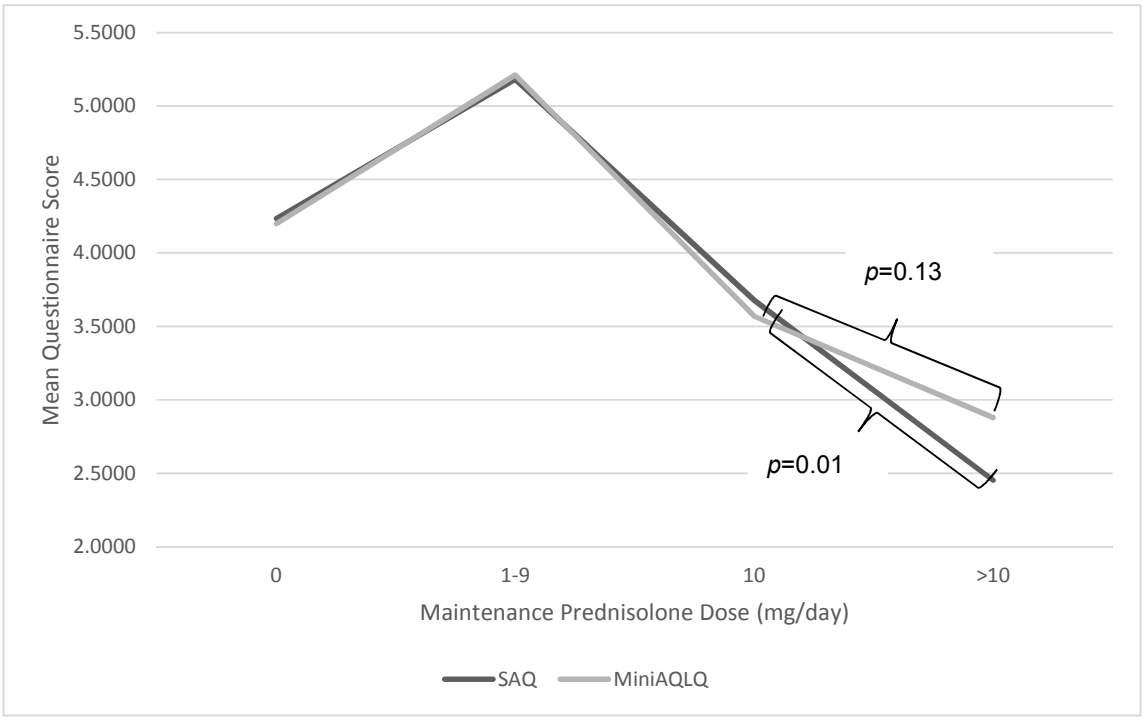

Figure 1. Mean SAQ and MiniAQLQ scores as a function of maintenance prednisolone dose (mg/day). When comparing 10mg to >10mg/day of maintenance prednisolone use, the SAQ detects a statistically significant difference in mean questionnaire score, but the mini-AQLQ does not.

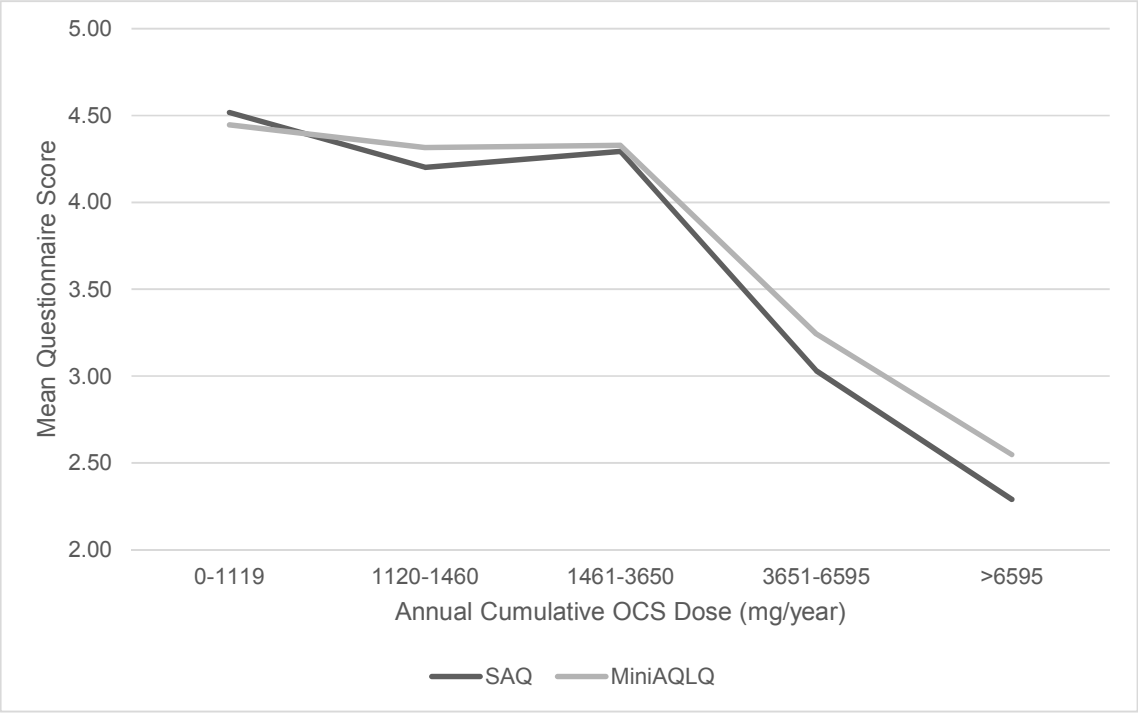

Figure 2. Mean SAQ and MiniAQLQ scores as a function of estimated annual cumulative OCS dose.

Online Supplementary Data

Content validity of the Severe Asthma Questionnaire from earlier studies

Findings of the initial patient interviews included (see [10] for more details)**:**

- Identification of domains that included deficits caused by symptoms of severe asthma as well as side effects of medication.
- A failure of existing asthma specific quality of life scales to assess all the domains to severe asthma.

Findings of the four focus groups included (see [13] for more details):

- The recall period of two weeks was acceptable, but a two week window fails to reflect the patients' desire to express the variability of severe asthma. Patients welcomed the ability to rate their global quality of life during the worst and best months of the year.
- Patients suggested improvements to the wording of the draft questionnaire, including splitting some items in two (the items relating to family life), combining two items in one (relating to appearance and embarrassment).
- Patients suggested changes to some of the words in individual items and the response scale.
- Patients can help optimise the language of a questionnaire better if they are treated as partners in the process of questionnaire completion rather than only as a source of information.

Criteria for incomplete questionnaires

For the SAQ and MiniAQLQ, questionnaires were considered incomplete if more than one question was missed excluding the question on work. In the case of the SAQ patients are instructed not to answer this question if not in work. In the case of the MiniAQLQ patients often miss this question even though they are instructed to answer it in terms of other activities if not in work. For the ACT a questionnaire was considered incomplete if one or more questions were missed. An EQ-5D-5L was considered incomplete if two of more questions were missed.

If patients are not in work, then the SAQ score is the average of the 15 lifestyle questions that do not refer to work. If patients are in work, then an extra domain is added because patients then have an extra domain of quality of life. Using this procedure, the non-work domains are the same for in and out of work patients. In the case of the MiniAQLQ, if patients are not in work, then they are asked to answer the work question in terms of other activities. Although the average MiniAQLQ score is obtained from the same number of questions for in work our out of work patients, the non-work domains no longer the same for in and out of work patients because the out of work patients are answering an additional non-work domain. An aim of content validity is to ensure that questions are interpreted in the same way by different patients. The procedure used by the SAQ achieves this aim and removes the inconsistency of some out of work patients completing the work item of the MiniAQLQ and some not doing so, which in the present study was 25 out of 160 participants.

Table E1.

SAQ response option frequencies

Item	1	2	3	4	5	6	7	Missing
1. My social life. For example: visiting friends, walking with friends, talking with friends, going to bars/restaurants, and parties.	14	26	26	28	21	15	29	1
2. My personal life. For example: washing, dressing, looking after myself, love life.	6	18	21	21	18	15	61	0
3. My leisure activities. For example: walking for pleasure, sports, exercise, travelling, taking vacations.	25	35	31	19	17	14	19	0
4. My jobs around the house. For example: housework, shopping, home maintenance, gardening.	17	26	28	26	19	21	21	2
5. My work or education. For example, missing days, can't do all I want to do.	18	18	14	18	13	13	34	32
6. My family life – how it affects me. For example: caring for children, family responsibilities	10	20	23	20	17	23	40	7
7. My family life – how it affects others. For example: others taking time off work, problems with childcare, family members becoming upset.	10	18	26	19	9	17	54	7
8. Depression. For example, feeling sad, fed up, blue.	16	29	23	20	23	19	25	5
9. Irritable. For example, snap at people, get angrier than I should.	17	27	23	27	16	22	26	2
10. Anxiety in general. For example, worry about things, always on edge.	23	24	27	15	16	26	27	2

11. Worry that asthma may get worse. For example, medicines no longer help, more frequent attacks.	21	41	23	14	21	14	24	2
12. Worry about long term side effects of medicines. For example, worry about cataracts, diabetes, bone fracture.	27	26	17	23	17	20	27	3
13. Worry about long term side effects of medicines. For example, worry about cataracts, diabetes, bone fracture.	38	32	32	15	15	15	11	2
14. Problems at night. For example, difficulty going to sleep, being woken very easily, waking often at night.	31	31	25	20	17	18	16	2
15. The way I look. For example, my weight, my skin bruises easily, using medicines in public, other people judging me	35	28	20	17	16	16	26	2
16. Problems with food. For example, I find I get very hungry, I just can't stop eating, stomach problems (e.g., pain, bloating, etc.)	21	21	13	28	18	25	31	3

Response options: 1 = very, very difficult (worst possible); 2 = very difficult; 3 = difficult; 4 = moderately difficult; 5 = slightly difficult; 6 = very slightly difficult (just noticeable); 7 = no problem

Table E2.

Intra-class correlation, confidence intervals and *n-values* for the 16 items of the SAQ

Item	Intra-class correlation
1. My social life. For example: visiting friends, walking with friends, talking with friends, going to bars/restaurants, and parties.	**0.89** 0.80-0.94 *50*
2. My personal life. For example: washing, dressing, looking after myself, love life.	**0.86** 0.75-0.92 *50*
3. My leisure activities. For example: walking for pleasure, sports, exercise, travelling, taking vacations.	**0.93** 0.88-0.96 *51*
4. My jobs around the house. For example: housework, shopping, home maintenance, gardening.	**0.88** 0.79-0.93 *51*
5. My work or education. For example, missing days, can't do all I want to do.	**0.87** 0.72-0.94 *27*
6. My family life – how it affects me. For example: caring for children, family responsibilities	**0.89** 0.81-0.94 *46*
7. My family life – how it affects others. For example: others taking time off work, problems with childcare, family members becoming upset.	**0.87** 0.76-0.93 *46*
8. Depression. For example, feeling sad, fed up, blue.	**0.85** 0.73-0.91 *51*
9. Irritable. For example, snap at people, get angrier than I should.	**0.85** 0.74-0.91 *51*
10. Anxiety in general. For example, worry about things, always on edge.	**0.84** 0.71-0.91

	51
11. Worry that asthma may get worse. For example, medicines no longer help, more frequent attacks.	**0.84** 0.73-0.91 *51*
12. Worry about long term side effects of medicines. For example, worry about cataracts, diabetes, bone fracture.	**0.66** 0.40-0.81 *50*
13. Worry about long term side effects of medicines. For example, worry about cataracts, diabetes, bone fracture.	**0.88** 0.78-0.93 *51*
14. Problems at night. For example, difficulty going to sleep, being woken very easily, waking often at night.	**0.84** 0.71-0.91 *51*
15. The way I look. For example, my weight, my skin bruises easily, using medicines in public, other people judging me	**0.86** 0.75-0.92 *51*
16. Problems with food. For example, I find I get very hungry, I just can't stop eating, stomach problems(e.g., pain, bloating, etc.)	**0.77** 0.59-0.87 *50*

Table E3. Relationship between SAQ and SAQ-global scores

SAQ-global score and descriptors* of quality of life	Number of patients	Mean SAQ score** (**SD**)
0-9 Extremely bad	4	1.5 (**0.6**)
10-19 Very bad	6	3.0 (**1.9**)
20-29 Bad	10	2.0 (**0.7**)
30-39	12	2.7 (**1.0**)
40-49 Somewhat bad	26	3.3 (**0.7**)
50-59	21	3.8 (**0.8**)
60-69 Moderately good	19	4.3 (**1.5**)
70-79 Good	31	4.8 (**1.1**)
80-89 Very good	17	5.5 (**1.6**)
90-100 Nearly perfect/Perfect	8	6.4 (**0.9**)

*****The position of descriptors is approximate in relation to numbers. The exact position is shown in the SAQ.

** Interpretation of mean: 1 = very, very difficult (worst possible); 2 = very difficult; 3 = difficult; 4 = moderately difficult; 5 = slightly difficult; 6 = very slightly difficult (just noticeable); 7 = no problem