University Hospitals Plymouth NHS Trust

SAQ
Severe Asthma Questionnaire (Quality of Life)

NATIONAL VALIDATION AND SENSITIVITY TO CHANGE OF A SCALE TO MEASURE QUALITY OF LIFE IN PATIENTS WITH SEVERE ASTHMA

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Sponsor

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The Proposal

This proposal describes the planned programme of research and provides information about study design. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study.

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Study Summary

TITLE	Further validation and determination of the Minimum Clinically Important Difference of a scale to measure quality of life in patients with severe asthma
DESIGN	A multi-centre mixed methods study of a new asthma specific quality of life questionnaire including limited clinic data, using the UK Severe Asthma Network.
AIMS	To collect further quantitative data to validate a new asthma quality of life scale, the Severe Asthma Questionnaire (SAQ). To determine the Minimum Clinically Important Difference (MCID) of the SAQ
OUTCOME MEASURES	Questionnaires: 1. The Severe Asthma Questionnaire (SAQ) 2. The Mini Asthma Quality of Life Questionnaire (MiniAQLQ) 3. The EQ-5D-5L 4. The Asthma Control Test (ACT)/ Asthma Control Questionnaire (ACQ) 5. Global Rating of Change Questionnaire (GRCQ) 6. Clinical data comprises: 7. Spirometry 8. BMI 9. Asthma severity 10. Health care utilisation: ED attendance in the last 12 months, Hospital admissions in the last 12 months; 11. Number of exacerbations in the last 12 months requiring OCS Prednisolone dose mg/day (if oral steroid dependent).
POPULATION	All patients aged 16 years or over, who have attended one of three participating UK specialist asthma centres for the validation study and with data also collected from Derriford Hospital's Chest Clinic (DHCC) for use in determining Minimum clinically Important difference.
ELIGIBILITY	Over 16 years of age Diagnosis of Severe Asthma
DURATION	18 months
REFERENCE DIAGRAM	Gantt chart (Appendix 1)

1. Introduction

1.1 Background

The global prevalence of asthma is estimated to be 300 million and is expected to grow by more than 100 million by 2025 [1]. 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 [2]. These patients have ongoing daily symptoms despite maximal medical therapy and are more likely to be admitted to hospital and to access out of hours' emergency healthcare than asthmatics with mild or moderate disease [2].

Corticosteroids have proved extremely effective in the acute and chronic treatment of inflammatory diseases. However, despite their clinical success, oral corticosteroids (OCS) have many known side effects which limit their tolerability, particularly in the long term [3]. As the multi-faceted negative consequences of OCS therapy are becoming better understood, the drive to find OCS substitutes becomes more urgent. However, in order to fully appreciate the value of steroid sparing agents which tend to be more expensive than OCS, the wider picture of OCS adverse effects must be considered to determine the real cost offsets achievable by such therapies.

While patients with mild and moderate asthma can usually be controlled using inhaled medication, in severe asthma OCS are often required. OCS exposure may be significant through either frequent short courses for exacerbations or as a maintenance dose. Studies on patients with mild and moderate asthma show that exacerbations are predicted by non-asthma related health problems [4] and by poor adherence [5]. In mild and moderate asthma, adherence to inhaled corticosteroids is affected by real or perceived medication side effects [6,7]. There is limited understanding of this relationship in severe asthma patients; qualitative data suggests that side effects impact on OCS use [7], but the relationship between OCS and inhaled medication adherence is complex [8]. Patients' concerns differ from those of clinicians [7,8]. The consequences of poor adherence for those with severe asthma are extremely serious and include frequent disabling attacks, recurrent unpredictable admissions and death.

While the consequences of non-adherence to OCS in patients with severe asthma may be dire, so too are the perceived side-effects. Of major concern to patients are changes in facial and body appearance, weight gain, gastro-oesophageal reflux, mood changes and sleep disruption. Metabolic changes including high blood pressure, precipitating diabetes mellitus and long-term effects on bone are of more concern to clinicians.

Health-related quality of life (HRQoL) is one of several outcome measures used to inform treatment guidelines and economic decision-making for the treatment of asthma. HRQoL scales are important amongst outcome measures in that they inform whether treatment is worthwhile from the perspective of the patient, a perspective that includes the burden of disease and the burden of treatment. Asthma varies in severity, and increased doses or types of medication are required for the more severe patients. Severe asthma patients have uniquely different types of HRQoL deficits and in this population the

burden of treatment, particularly with OCS, becomes a larger determinant of HRQoL. The impact of OCS is known to be far greater than the impact of other asthma treatments [8], and therefore, severe patients, i.e. those exposed to high doses of OCS, are likely to have a greater treatment burden than other patients.

Novel biologic agents are likely to become increasingly available to treat severe asthma. While these are more expensive than conventional treatments, if effective they may reduce symptoms, health care costs and reduce the need for oral steroids. In order to understand the impact of these newer drugs, measures must be used to accurately reflect the specific issues of severe asthma burden, including the burden of treatment. Previous work has demonstrated that existing asthma-specific scales underestimate the burden of severe asthma, in particular treatment with OCS, and therefore will underestimate the benefits of steroid sparing agents [8]. Improved assessment procedures are needed to provide accurate information on which treatment and resourcing decisions are made.

Research into severe asthma is limited by the lack of questionnaires suited to this population that capture both the health deficits experienced by severe asthma sufferers and the range of adverse experiences from treatment. It is therefore important that appropriate outcome and adherence measures are available to assess service development in relation to severe asthma. As a first step in questionnaire development, in-depth interviews were held in a sample of 23 patients attending the difficult asthma service at Derriford Hospital. These interviews revealed the substantial burden of symptoms associated with OCS that were not addressed by existing measures of health-related quality of life (HRQOL) [8].

The importance of such measures is emphasised by two major reports. The National Institute for Health and Care Excellence (NICE) is strongly supportive of the need for improved measurements which reflect the patients' burden in severe asthma and the impact of OCS [9]: "the Committee concluded that other adverse effects (of oral steroids), such as obesity, hypertension, mood changes, depression, psychosis, thinning skin, delayed wound healing, reduced growth in children and increased risk of infection were additional important factors that had not been captured when calculating the quality adjusted life years."

When statutory bodies such as NICE compare the cost effectiveness of very cheap OCS versus novel biologic agents, it is possible to conclude that such treatments may not meet the Incremental Cost-Effectiveness Ratio (ICER), particularly when compared to OCS. Only if the burden of OCS is accurately measured can the real cost effectiveness be established.

In a qualitative study [8] in-depth interviews were held in a sample of 23 patients attending the difficult asthma service at Derriford Hospital. The main health deficits and burden of treatment were defined and compared to existing questionnaires. We found just how much patients suffer from side-effects of long-term oral steroids and how these are poorly captured by existing scales. The National Review of Asthma Deaths [10] showed that asthma has many preventable factors, in particular, poor use of preventer medication. In addition, psychosocial factors such as depression contributed to the cause of death in 25% of cases. OCS have profound psychosocial impacts. Since the publication of this report, there has

been increasing interest in identifying people at risk of asthma deaths, improving services for patients with severe asthma, and rational use of new treatments.

The SAQ questionnaire was derived from a qualitative study [8] and questions and design were evaluated by a panel of international expert clinicians. The concepts and wording were modified and tested in an iterative series of four focus groups of patients attending the difficult asthma service [9]. The questionnaire was then field tested in 160 patients and compared to the MiniAQLQ, the Asthma Control test and clinic data including BMI, lung function, and health care consumption [10]. The final version takes into account the lessons learned from this quantitative study and further input from the panel of experts.

The SAQ questionnaire has 16 questions rated on a 0-6 Likert scale and on a 0-100 scale rating of (i) overall quality of life (ii) how your asthma symptoms and the side effects of your medicines have affected your quality of life during the last two weeks.

1.2 Rationale For Current Study

This research is the continuation of a project which provided preliminary validation of the SAQ. Whilst the preliminary validation provided evidence for the validity of the SAQ, a limited sample size made comparisons between groups of participants difficult. In addition, all data were collected in the South West of England (Plymouth, Devon), which may limit the studies generalisability to the rest of the UK. This further validation study will address these two issues by collecting more data from multiple centres around the UK. The second part of this research will collect data for the calculation of the SAQ's Minimum clinically Important difference (MCID). This value is required if the SAQ is to be useful in clinical practice, clinical trials and research.

Research into the burden of severe asthma, in particular treatment with OCS, is limited by the lack of questionnaires suited to this population that capture both the health deficits experienced by severe asthma sufferers, and the range of adverse experiences from treatment. As a consequence, the benefits of steroid sparing agents are underestimated [8].

NICE has called for such a questionnaire to measure the impacts on patients of severe asthma and its treatment. The new biological treatments which are already developed or in the pipeline need to be tested with measures which reflect their impact specifically on people with severe asthma [11]. Content validity of the SAQ has been established through the qualitative studies as recommended by the FDA [12].

The aim of this study is to provide further construct validity for the SAQ using UK collaborators. This will be done by showing that the SAQ is sensitive to differences in treatment, symptomatology, as well as being able to detect changes in patients' HRQOL after the commencement of a new treatment for severe asthma.

1.3 Patient And Public Involvement

Patients have been involved in the development of this questionnaire since the beginning of the research. As part of an initial study to identify the burden associated of living with severe asthma, qualitative interviews were conducted. In total 23 patients diagnosed with severe asthma were interviewed, and highlighted the burden they experienced as a result of taking OCS [8].

Furthermore, four focus groups were conducted in which patients were presented with a draft version of the Severe Asthma Questionnaire (SAQ). In total 16 patients diagnosed with severe asthma were recruited [9]. These patients gave substantial feedback concerning the wording of questions and the response scale used on the questionnaire. Participants also suggested the addition of new items to the questionnaire, in order to better capture the burden associated with their disease or OCS.

After gaining feedback from a panel of international expert clinicians, the wording of an item in the SAQ was changed to reflect a timescale of months, rather than seasons. This change was made in order to make the questionnaire internationally applicable, including in countries where they do not have four seasons.

It was decided by the SAQ development team that this constituted a significant change to the questionnaire. Therefore, this final version of the SAQ was also presented to four patients diagnosed with severe asthma, to check that this change had not altered the ease at which the focus group patients had understood the wording of the original questionnaire item.

Moreover, as this occurred in a clinic setting, this enabled us to ensure that patients found the SAQ as easy to complete in a clinic setting, which has considerable time constraints, compared to during the focus groups, where time was not a concern. Overall, these four patients reported that the final version of the SAQ was easy to comprehend and complete before their clinic appointment.

Potential logos for the SAQ were also discussed with five patients diagnosed with severe asthma, whilst they waited for their clinic appointment. The final logo was chosen as it was described as distinguishing the questionnaire from others. The patients' choice of logo was also considered by three specialist asthma nurses, who agreed that it would increase the chance of identifying the SAQ under the time constraints of day to day clinical practice.

Finally, the design and concept of the questionnaire and this study were discussed with the Plymouth Breathe Easy group of the British Lung Foundation who provided positive comments (7.2.17). These varied and extensive forms of qualitative evaluation were carried out in order to ensure content validity of the scale as defined by the FDA, where it is asserted that "Content validity is supported by evidence from qualitative studies that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use. Content validity is specific to the population, condition, and treatment to be studied [12].

2.0 National Validation Study

2.1 Aim

To further validate the SAQ for use in the United Kingdom.

2.2 Objectives

To collect data from patients attending the UK specialist Asthma centres:

To provide a description of the factor structure of the SAQ and to demonstrate equivalence across populations.

To show that the SAQ correlates in an acceptable manner with the Mini Asthma Quality of Life Questionnaire (MiniAQLQ) and EQ-5D-5L (EQ5D)

To show that the SAQ is a discriminator of patients who have different frequencies of exacerbations and different levels of prednisolone consumption.

To show that the SAQ is equivalent in discrimination for exacerbations to the MiniAQLQ or EQ5D but is a better discriminator than these questionnaires for treatment levels of oral corticosteroids.

2.3 Study Design

Type of study: A multi-centre, cross-sectional study of four questionnaires including clinic data.

Duration of the study: 12 months.

Sample size: 80 – 107 participants from each of the three centres (N= 240 - 321):

Royal Brompton and Harefield NHS Foundation Trust, London, UK

Birmingham Heartlands Hospital NHS Foundation Trust, Birmingham, UK

University Hospital of South Manchester, Manchester University NHS Foundation Trust, UK

Royal Devon and Exeter Hospital NHS Foundation Trust, Exeter, UK

2.4 Study outcome measures

2.4.1 Questionnaires:

Severe Asthma Questionnaire (SAQ) (Appendix 2)

The new questionnaire will provide a combined assessment of disease and its treatment on the quality of life of patients with severe asthma. The scale is based on existing HRQoL scales but modified for the severe population and provides separate assessments of the effect of asthma symptoms and the effect of asthma medicines. The questionnaire has 16 items and was produced from detailed qualitative research. An additional 3 items are included to asses overall QoL, and QoL during different months of the year [13].

EQ-5D-5L (Appendix 3)
This is a 5-item scale, with a final question which asks patients to use a category rating scale to rate their quality of life on the day of completion. This scale is commonly used in clinical trials to determine improvement in patients' perceived quality of life. The correlations between EQ-5D-5L scores and SAQ scores will be explored [14].

Routine Clinic Questionnaires
The Mini Asthma Quality of Life Questionnaire (MiniAQLQ) (Appendix 4)
This 15-item scale is commonly used as the quality of life scale in asthma studies [15]. For the purpose of validation, we wish to show that this scale correlates with the burden of symptoms but not, or with a much lower correlation, with the burden of treatment.

Asthma Control Test (ACT) (Appendix 5)
This 5-item scale is commonly used as a measure of asthma control in asthma studies [16]. For the purpose of validation, we wish to show that this scale correlates with the burden of symptoms but not, or with a much lower correlation, with the burden of treatment.

OR (depending on the preference of centres)

Asthma Control Questionnaire (Asthma Control Questionnaire) (Appendix 6)

Another questionnaire of asthma control. This questionnaire contains 7 items and takes into consideration FEV1% predicted and daily use of rescue bronchodilator. Patients respond to 7 items concerning their symptom severity on a 0-6 scale (0 = no impairment, 6 = maximum impairment) [17]

2.4.2 Clinic Data to be collected:

Data to describe patient characteristics

Patient demographics:

Age

Sex

Ethnicity

Clinical data:

Spirometry: absolute Forced Expiratory Volume (FEV1) (litres) and percentage of predicted FEV1 (FEV1%)

Forced Vital Capacity (FVC) (litres)

Weight (Kg), Body Mass Index (BMI)

Asthma severity: Treatment level by drug class classified by GINA step

Health care utilisation:

Emergency Department, attendance in the last 12 months

Hospital admissions in the last 12 months

Clinic Data Outcome Measures:

Number of exacerbations in the last 12 months requiring OCS

Prednisolone dose mg / day if on maintenance OCS

Note: The three UK specialist centres are part of the BTS severe asthma network, and contribute to a shared database. Except for the two study questionnaires (SAQ and EQ-5D-5L) the above data are part of routine data collection.

Permissions will be obtained following procedures appropriate for each centre.

2.5 Patient Invitation Letter and Patient Information Leaflet

As this study is taking place at multiple sites, the Patient Invitation Letter and Information Leaflet will need to be adapted for use by each centre. The anticipated adaptations will include: letter heading; and a change of the centres PI and research nurse contact details in the case that a participant has questions.

2.6 Recruitment and consent.

Patient eligible to participate in the study will be identified by a health care professional familiar with them. When possible, a Patient Invitation Letter (Appendix 7) and a Patient Information Leaflet (Appendix 8) will be posted to eligible patients two weeks before their scheduled clinic appointment. The Invitation Letter and Information Leaflet will provide patients with instruction to read the information carefully and to decide if they wish to participate in the study. The Information Leaflet will contain contact details for the patients clinical care team, as well as the SAQ development team in case the patient has questions. If they understand the information they have read and wish to participate, the Information Leaflet asks patients to sign the consent form and bring it with them to their next scheduled clinic appointment.

Alternatively, patients will be approached by a member of their clinical care team and asked if they wish to participate in the study during a clinic appointment. Patients will be provided with a Patient Information Leaflet at this time and given time to read through it and have any questions answered by *either* a healthcare professional responsible for their care before consenting *or* a member of the SAQ development team. When ready, the patient will be asked to sign the Consent Form.

The right of the participant to refuse to participate without giving reasons will be respected. All participants are free to withdraw at any time from without giving reasons and without prejudicing further treatment.

2.6.1 Inclusion Criteria

All patients must have a diagnosis of severe asthma, be taking high dose inhaled corticosteroids (GINA step 4 & 5), and be aged 16 years or over.

2.6.2 Exclusion Criteria

Patients that are unwilling to participate will be excluded from the study.

In the opinion of the physician responsible for the care of the patient, the patient has a condition, other than asthma, which is significantly contributing to their respiratory symptoms, e.g. lung cancer, heart failure or severe COPD.

The SAQ is currently only translated into British English. Therefore, if the participant is unable to read in English, they will be unable to participate.

2.6.3 Sample size calculation

Sample size determination is based on the analysis where the greatest number of patients is needed, namely factor analysis. For exploratory factor analysis the number of participants needed per item varies but ranges between 15 and 20 participants per item [18, 19]. There are 16 items in the SAQ. Thus, data from 240 – 320 participants is needed for any factor analysis, (80 – 107 participants from each centre.)

2.7 Data Collection Method

After providing written informed consent, participants will be provided with a pack consisting of a consent form, and the following questionnaires: (a) SAQ, (b) MiniAQLQ, and (c) EQ-5-5L (d) ACT/ACQ.

All clinic data will be input onto the Baseline Case Report Form (CRF) (Appendix 9) by a research nurse. This data and the completed pseudonymised questionnaires will be emailed to the Plymouth RA (JL) *via* NHS email. This data will utilise a participant number system. Each site will place a copy of the completed questionnaires into the patient's notes as they may contain relevant clinical information for current and future treatment.

2.8 Analysis

Factor analysis of the SAQ A trial principal axis factor analysis with scree plot will be calculated. On the basis of factor loadings on the first factor, it will be decided whether it is legitimate to provide an overall score for the questionnaire. Using the scree plot to determine factor number, an oblique rotation will be carried out and interpretation of emerging factor loadings (from the pattern matrix) determined. Correlations between questionnaires

Correlations between questionnaires will be calculated using Pearson Correlations.

Discriminant validity We will test for significant differences between the SAQ and other scales using a mixed design analysis of variance (one within and one between) where groups are defined in two ways (a) maintenance dose oral corticosteroids and (b) cumulative dose oral corticosteroids. The aim of this analysis is to investigate whether the SAQ has better discriminant validity than other scales. First the interaction term of the analysis of variance will be used to determine whether sensitivity differs across all groups. Second, because the SAQ is expected to be more sensitive to discrimination at the top end of prednisolone use, a mixed design analysis of variance will be conducted on the two highest doses of prednisolone only.

3.0 Sensitivity to Change Study

3.1 Aim

To assess the sensitivity to change of the SAQ, for patients who initiate a new biologic treatment for their asthma.

To determine the SAQ's minimal clinically important difference (MCID).

3.2 Study Design

Type of study: A multi-centre sensitivity to change study, using the SAQ, other questionnaire measures and clinic data

Duration of the study: 18 months.

Sample size: Between 30 and 50 participants per each of the five participating sites:

1. University Hospitals Plymouth, NHS Foundation Trust, Plymouth, UK
2. Royal Brompton and Harefield NHS Foundation Trust, London, UK
3. University Hospital of South Manchester, Manchester University NHS Foundation Trust, UK
4. Birmingham Heartlands Hospital NHS Foundation Trust, Birmingham, UK
5. Royal Devon and Exeter Hospital NHS Foundation Trust, Exeter, UK

Baseline questionnaire data from participants recruited for this part of the study will be added to the dataset for part 1.

3.3 Study outcome measures

3.3.1 Investigation questionnaires:

1. Severe Asthma Questionnaire (SAQ) (Appendix 2)
2. Global Rating of Change Questionnaire (Appendix 10)
   This scale will be used by participants to indicate how much better they feel since commencing a biologic treatment for asthma. The 11-point scale ranges from -5 (a great deal worse) to 5 (A great deal better) [20].
3. EQ-5D-5L (Appendix 3)

3.3.2 Clinic Data to be collected:

Baseline characteristics:

Age

Sex

Spirometry: absolute FEV1 (litres) and percentage of predicted FEV1 (FEV1 %)

Forced Vital Capacity (FVC) (litres)

Body Mass Index (BMI)

Asthma severity: Treatment level by drug class classified by GINA step

Maintenance OCS dose (mg/day)Health care utilisation:

Emergency Department attendance in the last 12 months

Hospital admissions in the last 12 months

Clinic Data Outcome Measures to be recorded at each treatment visit:

Weight (Kg)

Maintenance OCS dose (mg/day)

Number of exacerbations since last clinic visit requiring OCS Health care utilisation, the number of:

Emergency Department attendances since last clinic visit

Hospital admissions since last clinic visit.

Must be recorded on the follow-up CRF at the final study visit (16 weeks), (weeks 4, 8 and 12 are optional):

FEV1 (litres)

FEV1 (% predicted)

3.4 Recruitment and Consent

Patients will be identified as eligible to participate by a health professional familiar with them. When possible, these patients will be contacted by a health professional two weeks before they are due to attend for their asthma treatment, and invited to participate. This contact will be made by posting a Patient Invitation Letter (Appendix 11) and Patient Information Leaflet with a consent form (Appendix 12) out to the patient.

The Invitation Letter and Patient Information Leaflet will include instructions to read the material carefully. Contact details for the centres PI, and researcher will be included on the Patient Information Leaflet, and can be contacted if the patient has questions. If they wish to participate after reading this information, patients may complete the consent form and bring it with them to their next asthma clinic appointment.

Alternatively, when attending their appointment, patients who have been identified as eligible to participate in this study, will be asked if they are interested in participating. If so, a health professional will brief and consent the patient or alternatively, will introduce the patient to a researcher who will facilitate this. The participant will be provided with a Patient Information Leaflet. The patient will be assigned a participant number at this time.

The researcher will be available to answer detailed question about the research project. In addition, as this is a clinic setting, multiple health professionals will also be present, who will be aware of this project, and be able to answered questions, or refer the patient to the researcher if necessary. Patients will have all questions answered, before they sign a consent form, and will be aware that they can withdraw at any time if they choose.

3.4.1 Inclusion Criteria

Patients commencing a biologic treatment for their severe asthma (GINA step 4 & 5), as per NICE guidelines

3.4.2 Exclusion Criteria

Patients will be excluded from the study if they are unwilling to participate

In the opinion of the physician responsible for the care of the patient, the patient has a condition, other than asthma which is significantly contributing to their respiratory symptoms, e.g. lung cancer, heart failure or severe COPD.

3.4.3 Sample size calculation

Three types of analysis are planned. Sample size is based on analysis 2 (see below where the sample is divided into quartiles and we test whether there are significant differences between quartiles. Four groups of 25 patients will detect an effect size of 0.3 with a power of 70% at a significance level 5%. The total sample is therefore 100 participants. The addition of a fifth site with the aim of also recruiting 25 patients will mean this analysis remains sufficiently powered even if one of the other sites under-recruits.

3.5 Data collection methods

After providing written informed consent, patients commencing a new biologic treatment for their severe asthma will be asked to complete the SAQ (Appendix 2) and the EQ-5D-5L (Appendix 3) at the time of their first treatment. This is in addition to the Mini Asthma Quality of Life questionnaire (Mini-AQLQ) (Appendix 4) and Asthma Control Test (ACT) (Appendix 5) **or** Asthma Control Questionnaire (ACQ) (Appendix 6), which are normally completed as part of an appointment.

As this is a new biologic treatment, patients will be expected to attend a hospital appointment every 2 or every 4 weeks for subsequent treatments. The frequency of these visits is dependent on the biologic treatment that is prescribed.

In total there are five questionnaires. Participants will not be asked to complete all five at every visit. At 4, 8, 12 and 16 weeks participants will be asked to complete the Severe Asthma Questionnaire (SAQ) and the Global Rating of Change Questionnaire (GRCQ). At sixteen weeks participants will be asked to complete the EQ-5D-5L again in addition to the SAQ and GRCQ.

Once completed, the pseudonymised questionnaires will be scanned and sent to the Plymouth RA (JL) *via* NHSmail after each appointment.

Demographic Information and clinic data from week 0 (baseline) will be entered into the Baseline CRF (Appendix 9). Once completed, the Baseline CRF will then be scanned and sent to the Plymouth RA (JL) *via* NHSmail. Data collection from appointments at 0, 4, 8, 12 and 16 weeks will be entered into the Follow-up CRF (appendix 13). Once complete, the Follow-up CRF will be scanned and sent to the Plymouth RA (JL) *via* NHSmail.

Participant data from week 0 (baseline) will be added to the validation dataset. This will be explained to the patient on the Patient Information Leaflet (Appendix 12).

Copies of the questionnaires will also be placed in the patients' medical file at the participating site.

3.6 Analysis

The SAQ provides two scores, the SAQ score which is the mean of all 16 domain specific items, and the SAQ-global score which is a single item score based on the SAQ-Global, which itself is based on a Borg scale [21]. Borg scales use multiple quantifiers at empirically derived points along the scale with the aim of achieving a ratio scale. In this analysis plan, the term SAQ will refer to both the SAQ score and the SAQ global score. Separate analyses will be carried out on the SAQ score and SAQ-global. Several analyses will be carried to ensure that the MCID concept is fit for purpose.

Data from 4, 8, 12 and 16 weeks will be compared to the data collected at week 0 (baseline), providing 4 change scores per patient. Patients can indicate any one of 5 levels of improvement in any of the four weeks, or, if there is no change or deterioration, up to 11 types of change. If patients report the same level of global rating of change at each of the four time points (e.g., they record 'a little better' at week 4 and 'a little better at week 8), the average SAQ change score will be calculated for that patient. This average will then be used as the SAQ change for that particular level of global rating of change. This procedure is followed so that each patient can contribute just one value to the population average of the SAQ change score at any level of global change, and which, in the case of the level of 'a little better' is used to calculate the MCID. We shall carry out three analyses to check on the validity of the MCID concept. If the checks come out positive, then the existing method of calculating the MCID (i.e., as the change in the SAQ that maps on to the global rating of change criterion of 'a little better) will be adopted.

If the checks are negative – i.e., suggesting some revision to the way the MCID concept is employed – then we will adapt the methodology in accordance with our findings.

What degree of change on the SAQ is associated with each of the 5 levels of improvement and 5 levels of deterioration on the global rating of change score?

The mean, confidence intervals, and standard deviation of change of the SAQ will be calculated for each level of change in the GRCQ. These means will then be plotted (change in SAQ on x axis, global change on y axis) to show the relationship between change and perceived change at different degrees of change. These results should show that the change in the SAQ increases with increase in global change scores, and will be tested for by analysis of variance. This analysis is needed to show that the MCID is specific to the level of change of 'a little better' or 'a little worse' rather than any other level of global rating of change. The analysis will also check whether 'a little better' is equivalent in terms of 'a little worse' in terms of SAQ change.

Is the MCID transitive– i.e., is the MCID independent of level of deficit of quality of life?

Patients will be allocated to quartiles based on severity of the SAQ score at week 0. The mean, confidence intervals and standard deviation of change scores for change at 'a little better' will be calculated. Analysis of variance will be calculated for the four quartiles to test of transitivity. Effect size (eta) will be calculated. This analysis is needed to show that the MCID level can be applied across the full range of deficit of quality of life.

Are items in the SAQ equivalent with regard to the MCID – i.e., is change in all the 16 SAQ items equivalent in terms of their relationship with the global rating of change?

To test for equivalence, change in each of the 16 items of the SAQ and the SAQ-global will be correlated against the global rating of change score. These correlations will be examined and interpreted. Regression will be explored, but may be ruled out due to co-linearity. This analysis is needed to show whether weighting of items is needed when calculating the MCID, or whether the MCID is based simply on the mean of all items.

Demographic information analyses

In addition, we will also test whether baseline characteristics are similar across the four quartile groups and investigate whether the change in SAQ is related to the collected demographic and clinical data.

If the above show no problems with the existing methodology, then the MCID will be calculated from the average SAQ change for the rating of 'a little better'. That is, any patient who has provided a global rating of change of 'little better' will contribute an initial and final SAQ score to produce a SAQ difference score for each patient, and the average of the SAQ difference scores across patients will be then form the MCID. If there are problems, then we shall modify the MCID, for example, having different values for different levels of quality of life deficit (see 2 above) or by using a weighting of items (see 3 above).

4.0 Withdrawal Criteria for study programme

Whilst participating in the study, a patient's health or diagnosis may change. If this occurs during the study, the participant eligibility for the study they are in will be re-assessed. If the participant no longer meets the eligibility criteria, their data may be removed from the database. The patient will be thanked for their time, and told not to expect to be asked to participate further.

5.0 Data Management for study programme

The study incorporates the following types of data, which will only be accessed by the research team:

Quantitative data: Anonymised questionnaires, validating clinic data information;

Routinely recorded clinic data and service use in the last 12 months;

Recruitment data (proportions of uptake, completion and attrition).

In accordance with the Data Protection Act (2018), UHPNT information governance policy, all researchers will ensure that study participants' anonymity is maintained and data is stored securely. Study participants will be assigned a study ID number which will replace the patient's name on all data. Each centre will be given a different participant number pre-fix to use (see the table below). All data will

be password protected, stored securely and will only be accessible by researchers and authorised personnel from Plymouth University and UHPNT.

Table of participant numbers

Site	Participant number pre-fixes
Derriford Hospital	1.xxx
The Royal Brompton Hospital	2.xxx
University Hospital of South Manchester	3.xxx
Birmingham Heartlands Hospital	4.xxx
Royal Devon and Exeter Hospital	5.xxx

Anonymised electronic will be transferred to Plymouth University for analysis. It will be transferred from UHPNT to UoP by NHS email.

The sender will ensure that the NHS email encryption service is used. The University uses a secure shared drive which the study team will use to store electronic data. Printed anonymised data will be kept in project specific folders, stored in a locked cupboard in a locked room, under the responsibility of the Investigators.

After coding, the source questionnaires will be added to the patients' notes because they contain information which may be helpful to the clinical team. Patients' records are stored securely on UHPNT premises in accordance with UHPNT information security policy.

A document linking research IDs with clinical identification numbers will be created and stored within each of the patients' respective centres, anonymised data will be analysed by the SAQ team (RJ, MM, MH, JL and YW).

After the end of the study, anonymised information collected during the study will be made available to other researchers under an appropriate data sharing agreement, but it will not be possible to identify participants personally from any information shared.

5.1 Procedure for Accounting for Missing, Unused, and Spurious Data.

Questionnaires where the completion rate is < 10% will be defined as invalid, but the level of invalid data will be used to inform the development of the questionnaire (for example, individual items with large amounts of missing data will be scrutinised closely and may be amended or excluded from the future drafts of the scale). Data entry will be checked for 1 in 5 cases and more frequently if errors are found.

5.2 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Our study is not a trial. However, any additional analysis or deviations will be reported as such to the study management group and the independent study steering committee and other appropriate authorities as per GCP.

5.3 Archiving

Following completion of data analysis, the Sponsor will be responsible for archiving the study data and essential documentation in a secure location for a minimum period of 5 years after the end of the study. No study-related records should be destroyed unless or until the Sponsor gives authorisation to do so. Medical case notes containing source data or other trial-related information should be identified by a label “Keep until dd/mm/yyyy” where the date given is 5 years after the last participant’s final study visit.

6.0 Regulatory Issues

The Investigator will ensure that this study is conducted in full conformity with relevant regulations, the UK Policy Framework for Health and Social Care Research (2017) and in accordance with the principles of the Declaration of Helsinki.

6.1 Ethics Approval

The CI will obtain a positive opinion from a Health Research Authority (HRA) Research Ethics Committee (REC) for the study.

The CI will also require a HRA approval letter and a Capability and Capacity e-mail statement from the local R&D office before recruitment of participant’s into the study.

Any amendments to the study protocol will require review by HRA (and possibly the REC if the amendment is deemed to be substantial by the study sponsor) and will not be implemented until the HRA grants a favourable opinion for the amendment, which will also need to be reviewed and accepted by the NHS R&D department before they can be implemented in practice.

All correspondence with the HRA will be retained in the Trial Master File/Investigator Site File.

An annual progress report (APR) will be submitted to the HRA within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the CI’s responsibility to produce the annual reports as required. The CI will also notify the HRA and sponsor of the end of the study. If the study is ended prematurely, the CI will notify the REC, including the reasons for the premature termination.

Within one year after the end of the study, the CI will submit a final report with the results, including any publications/abstracts, to the HRA. The investigator will ensure that this study is conducted in full conformity with relevant national regulations and with the UK Policy Framework for Health and Social Care Research (2017). The research team will also bear in mind the principles of the Declaration of Helsinki when conducting the study.

6.2 Ethical Issues

We acknowledge the need to protect the dignity, rights, safety and wellbeing of participants taking part in this research study. Although the potential for harming participants as a direct result of being involved in the study are considered to be minimal, a contingency will be put in place, should a patient become distressed whilst taking part in the study. To begin patients will be made aware that the researchers are

not there as clinicians, but as researchers. Should any patient appear distressed as a result of completing the questionnaires, they will be given the opportunity to speak with a clinician. Should they have concerns about the conduct of the study, they will be given the contact details for the study CI and contact details for PALS, which will appear on the Patient Invitation Letter.

We appreciate the number of questionnaires patients are being asked to complete as part of the study and are keen to limit the burden of data collection. There are 41 questions in the four questionnaires taken together for part 1 of the study. Participants enrolled in part 2 of the study will not be asked to complete all five at their questionnaires at one occasion. At most they will be asked to complete three questionnaires. As part of their treatment for their asthma, patients on biologic treatments are asked to stay for at least 30 minutes following each injections so they can be monitored. The questionnaires can be completed during this time. This should take about 20 minutes.

6.3 Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and will comply with the Data Protection Act (2018). Research teams at all sites will ensure that participants' anonymity is maintained on all documents in compliance with national regulations. A privacy notice explaining how patient research data is used will be included in the Participant Information Sheet.

6.4 Indemnity

This is an NHS-sponsored research study. If an individual suffers negligent harm as a result of participating in the study, NHS indemnity covers NHS staff and those people responsible for conducting the trial who have honorary contracts with the relevant NHS Trust. In the case of non-negligent harm, the NHS is unable to agree in advance to pay compensation, but an *ex-gratia* payment may be considered in the event of a claim.

6.5 Sponsor

The study Sponsor is University Hospitals Plymouth NHS Trust (UHPNT). Selected sponsorship tasks will be formally delegated to the SAQ Team and study sites according to an agreed task allocation matrix.

6.6 Monitoring, Audit & Inspection

The study may be subject to monitoring by Universities Hospitals Plymouth NHS Trust under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research (2017). It's current policy that the R&D Office will monitor all studies sponsored by the Trust 30 days after approval of the study (from the date of Trust Capacity & Capability e-mail).

The research team will check completed study data collection documents for missing data or obvious errors before forms are sent to the SAQ Team. Data will be monitored centrally for quality and completeness by the SAQ Team and every effort will be made to recover data from incomplete forms

where possible. The SAQ Team will oversee data tracking and data entry and initiate processes to resolve data queries where necessary. The SAQ Team trial manager will devise a risk-based monitoring plan specific to the study which will include both central monitoring strategies and study site visits as appropriate.

7.0 Study Management

The CI will be responsible for the overall running of the trial and for the local conduct of the trial at the Plymouth site. The PI at each of the other participating sites will be responsible for the conduct of the study at his/her trial site. The sponsor will coordinate trial-related activities and assist with overall trial management, monitoring and production of progress reports.

The roles and responsibilities of each member of the research team are as follows:

Chief Investigator

Matthew Masoli – clinical and difficult asthma advice, use of questionnaire in clinical practice lead for dissemination at conferences etc.

Co-Investigators

Michael Hyland – questionnaire design and adaptations, and translations

Rupert Jones – study management and co-ordination, communications lead to GSK and wider communications strategy, advice on use of questionnaire in clinical practice, conference presentations

Statistician

Yinghui Wei

Study coordinator

Joseph Lanario

The research group is further supported by the Research Development and Innovation team of Universities Hospitals Plymouth NHS Trust including governance, and logistic support.

7.1 Study Management Group

A Study Management Group (SMG) including the CI, SAQ Team, trial statistician and other personnel relevant to the study (e.g. clinicians, patient and Sponsor representatives) will meet regularly (usually monthly) throughout the duration of the trial to monitor progress, resolve day-to-day problems, oversee development of study documentation, monitor participant recruitment and retention, assess data quality, review budgetary issues, discuss analysis, interpret study findings, draft reports and plan dissemination of results.

8.0 Dissemination and Publication Policy

A website for the Severe Asthma Questionnaire has been established, www.saq.org.uk. This website includes various pages containing versions of the questionnaire, information about how the SAQ was developed, advice on use and scoring, publications, contact details and translation etc.

After publication, the study team will prepare a plain English summary of the study results which will be posted on a website and each PI will be notified. As soon as practicable, patients at sites involved in the study will be informed of the results.

A formal worldwide communications strategy will be developed to promote the use of the SAQ including submissions to the FDA and other regulatory bodies. We will plan to ensure that key opinion leaders are well informed and will provide resources for promotion such as slide sets.

9.0 Funding

An unrestricted non promotional grant from GlaxoSmithKline

10.0 Impact

The proposed studies will produce the SAQ which will be validated furtherfor use in the UK:

The educational value for clinicians of understanding the impact of severe asthma on patients. The outputs of the research will demonstrate the differences in health issues for patients with mild-moderate asthma versus those with severe asthma. This will allow clinicians to ensure that the specific problems faced by patients with severe asthma are identified and can then be addressed and help patients to be referred appropriately.

In routine clinical practice in severe asthma services, having questionnaires to measure both the severe symptom burden and the burden of treatment will allow rational choices in the use of newer biological agents in severe asthma.

The choices will better reflect the patients' perspective. As this is a multi-centre study, the new questionnaire will get significant exposure to a large number of key severe asthma specialists and this will help its dissemination and adoption in clinical practice.

For research, especially in clinical trials of newer drugs, the questionnaire will allow better assessment of impacts which affect patients with severe asthma.

The questionnaire is expected to be more responsive to change. For example, if a drug allows a reduction in OCS exposure, the benefits can be more accurately measured particularly from a patient-centred perspective. In turn, if more accurate measurement of the burden of severe asthma and its treatment is performed in clinical trials, regulatory bodies such as NICE are better able to assess the true value of newer, but expensive, drugs (indeed, NICE has called for such measures to facilitate rational decisions on the use of relatively expensive therapies for patients who may benefit).

While the initial emphasis of this research proposal has been in the United Kingdom, the questionnaires are applicable to patient populations around the world as the issues confronting patients with severe asthma are similar. Where they can be afforded, novel biological agents may be used extensively globally. The questionnaires will help to identify those people who are likely to benefit from steroid sparing medications and measure the impact such medicines have on improving patient-related

outcomes. Given the enormous burden of severe asthma, it is imperative that the right measures are available to assess treatments for this group of patients.

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