

11. APPENDICES

11.1. Appendix 1: St. George's Respiratory Questionnaire

Background

The St. George's Respiratory Questionnaire (SGRQ) is an index designed to measure and quantify health-related health status in patients with chronic airflow limitation. It has been shown to correlate well with established measures of symptom level, disease activity and disability.

The first part ("Symptoms") evaluates symptomatology, including frequency of cough, sputum production, wheeze, breathlessness and the duration and frequency of attacks of breathlessness or wheeze. The second part has two components: "Activity" and "Impacts". The "Activity" section addresses activities that cause breathlessness or are limited because of breathlessness. The "Impacts" section covers a range of factors including influence on employment, being in control of health, panic, stigmatization, the need for medication, side effects of prescribed therapies, expectations for health and disturbances of daily life.

Administering the SGRQ

The SGRQ will be administered prior to all other scheduled procedures at designated visits.

The test is to be self-administered in a quiet room in the clinic away from friends, relatives and other patients. The patient must not be allowed to complete the questionnaire at home.

Patients should be handed the questionnaire by the clinic nurse or the study coordinator for completion. Ask the patient to complete it as honestly as possible and emphasize that there are no right or wrong answers; only the answer that best applies to them. Explain that they must answer every question and that a clinic nurse or study coordinator will be available to give advice if necessary.

Handling questions from patients

Answers to some possible questions are provided in the "Guide to Completing the SGRQ" section following the questionnaire. The study coordinator should review these guidelines before seeing patients to prepare for their questions.

If the patient asks for help answering a question, the study coordinator must not give them a direct answer. The goal of a health status questionnaire is to get an understanding of how patients view their own illnesses. It is advised to redirect the question to the patient.

Questions may be read to patients who have difficulty reading, but responses must be theirs alone.

Completing the SGRQ

When the patient has completed the questionnaire, the coordinator should review it to ensure that all questions have been answered. If any question is blank, double-check with the patient without being critical.

Note that this assessment is a co-primary endpoint in this study. Therefore, it is important that the SGRQ is fully completed by the patient.

If the study coordinator sees an answer that seems incorrect (e.g., the patient marks that he coughs a few days a month and it is documented that he coughs more often) do not question its accuracy. By questioning a patient's answer, the coordinator is basically telling the patient that he/she is wrong and the patient may change the original answer even though he/she feels it was correct.

A copy of the SGRQ as well as a Guide to Completing the SGRQ is provided on the following pages.

Reference

1. JONES PW, ET AL. 1992. A self-complete measure for chronic airflow limitation, the St. George's Respiratory Questionnaire. *Am Rev Respir Dis*, **145**, 1321-1327.

The St. George's Respiratory Questionnaire

This questionnaire is designed to help us learn more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problems, rather than what the doctors and nurses think your problems are.

Please read the questions carefully and ask the study nurse if you do not understand anything. Answer the questions as honestly as possible. There are no right or wrong answers; only the answer that best applies to you. Do not spend too much time deciding about your answers.

Part 1

Describe how often your lung/respiratory problems have affected you over **the last 4 weeks**. Please place a mark in one box for each question.

	almost every day	several days a week	a few days a month	only with lung/respiratory infections	not at all
1. Over the last 4 weeks, I have coughed:					
2. Over the last 4 weeks, I have brought up phlegm (sputum):					
3. Over the last 4 weeks, I have had shortness of breath:					
4. Over the last 4 weeks, I have had episodes of wheezing:					

5. During the **last 4 weeks**, how many severe or very unpleasant episodes of lung/respiratory problems have you had? Mark one answer only.

- _____ more than 3 episodes
- _____ 3 episodes
- _____ 2 episodes
- _____ 1 episode
- _____ no episodes

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6. How long did the worst episode of lung/respiratory problem last? Mark one answer only.

Go to question 7 if you didn't have a severe episode.

- a week or more
- 3 or more days
- 1 or 2 days
- less than a day

7. Over the last 4 weeks, in an average week, how many good days (with few lung/respiratory problems) have you had? Mark one answer only.

- None
- 1 or 2
- 3 or 4
- nearly every day
- every day

8. If you wheeze, is it worse in the morning? If you don't wheeze, go to Part 2.

- No
- Yes

Part 2

Section 1:

How would you describe your lung/respiratory condition? Mark one answer only.

- The most important problem I have
- Causes me a lot of problems
- Causes me a few problems
- Causes me no problem

If you have ever held a job, please mark one of these answers:

- My lung/respiratory problem made me stop my job.
- My lung/respiratory problem interferes with my job or made me change my job.
- My lung/respiratory problem does not affect my job.

Section 2: These are questions about what activities usually make you feel short of breath. Mark either True or False as it applies to you **now**.

	True	False
Sitting or lying still		
Washing yourself or dressing		
Walking in the house		
Walking outside on level ground		
Walking up a flight of stairs		
Walking up hills		
Playing sports or active games (baseball, tennis, etc.)		

Section 3: These are more questions about your cough and shortness of breath. Mark either True or False as it applies to you **now**.

	True	False
Coughing hurts.		
Coughing makes me tired.		
I am short of breath when I talk.		
I am short of breath when I bend over.		
My coughing or breathing disturbs my sleep.		
I become exhausted easily.		

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Section 4: These are questions about other effects that your lung/respiratory problem may have on you. Mark either True or False as it applies to you **now**.

	True	False
My coughing or breathing is embarrassing in public.		
My lung/respiratory problem is a nuisance to my family, friends or neighbors.		
I panic or get afraid when I cannot catch my breath.		
I feel that I am not in control of my lung/respiratory problem.		
I do not expect my lung/respiratory problem to get any better.		
I have become frail or an invalid because of my lung/respiratory problem.		
Exercise is not safe for me.		
Everything seems too much of an effort.		

Section 5: These are questions about your lung/respiratory medication, including oxygen, inhalers and pills. If you are not receiving medication, go to Section 6. Mark either True or False as it applies to you **now**.

	True	False
My lung/respiratory medication does not help me very much.		
I get embarrassed using my lung/respiratory medication in public.		
I have unpleasant side effects from my lung/respiratory medication.		
My lung/respiratory medication interferes with my life a lot.		

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Section 6: These are questions about how your activities might be affected by your breathing problem. For each item, answer True if one or more parts applies to you because of your breathing problem. Otherwise answer False.

	True	False
I take a long time to get washed or dressed.		
I cannot take a bath or shower, or I take a long time to do it.		
I walk slower than other people my age, or I stop to rest.		
Jobs such as household chores take a long time, or I have to stop to rest.		
If I walk up one flight of stairs, I have to go slowly or stop.		
If I hurry or walk fast, I have to stop or slow down.		
My breathing problem makes it difficult to do things such as walking up hills, carrying things up stairs, light gardening such as weeding, dancing, playing golf or light sports such as horseshoes.		
My breathing problem makes it difficult to do things such as carrying heavy loads, digging in the garden or shoveling snow, jogging or walking briskly, playing tennis or swimming.		
My breathing problem makes it difficult to do things such as very heavy manual labor, riding a bike, running, swimming fast or playing competitive sports.		

Section 7: We would like to know how your breathing **usually** affects your daily life. Mark True or False as it applies to you because of **your lung/respiratory problem**.

	True	False
I cannot play sports or active games.		
I cannot go out for entertainment or recreation.		
I cannot go out of the house to do the grocery shopping.		
I cannot do household chores.		
I cannot move far from my bed or chair.		

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Here is a list of other activities that your lung/respiratory problem may prevent you from doing. (You do not have to fill these in, they are just to remind you of ways in which your shortness of breath may affect you):

- Going for walks or walking the dog
- Doing activities or chores at home or in the garden
- Having sexual intercourse
- Going to church, or place of entertainment
- Going out in bad weather or into smoky rooms
- Visiting family or friends or playing with children

Please write in any other important activities that your lung/respiratory problem may stop you from doing:

Now, would you mark the one statement which you think best describes how your breathing problem affects you:

- It does not stop me from doing anything I would like to do.
- It stops me from doing one or two things I would like to do.
- It stops me from doing most of the things I would like to do.
- It stops me from doing everything I would like to do.

Thank you for filling out this questionnaire. Please check to be sure that you have answered all questions.

Guide to Completing the SGRQ

This is a guide to answering questions some patients may have as they complete the SGRQ. Suggested responses are provided in italics after the question or statement.

Part 1

Questions about how much chest trouble you have had over the last 4 weeks. Please place a mark in one box for each question.

Emphasize to the patient that we are interested in how many lung/respiratory problems he/she has had over the last 4 weeks. We are looking for an impression or perception of health.

	almost every day	several days a week	a few days a month	only with lung/respiratory infections	not at all
1. Over the last 4 weeks, I have coughed:					
2. Over the last 4 weeks, I have brought up phlegm (sputum):					
3. Over the last 4 weeks, I have had shortness of breath:					
4. Over the last 4 weeks, I have had episodes of wheezing:					

Check that one box has been marked for each question. Checkmarks may have been transposed to boxes either above or below the appropriate line. Check for double entries.

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5. During the **last 4 weeks**, how many severe or very unpleasant episodes of lung/respiratory problems have you had? Mark one answer only.

- more than 3 episodes
- 3 episodes
- 2 episodes
- 1 episode
- no episodes

"Severe or very unpleasant episodes of lung/respiratory problems" can be further described as "Whatever is a bad episode for you," in the patient's own judgment, not bad as defined as the doctor or nurse. Check that only one answer has been marked.

6. How long did the worst episode of lung/respiratory problem last? Mark one answer only.

Go to question 7 if you didn't have a severe episode.

- a week or more
- 3 or more days
- 1 or 2 days
- less than a day

Or, "How long did the most severe episode of lung/respiratory problem last?" This response should relate to item 5. If "no episodes" was the response for Question 5, this item will be blank.

7. Over the last 4 weeks, in an average week, how many good days (with few lung/respiratory problems) have you had? Mark one answer only.

- none
- 1 or 2
- 3 or 4
- nearly every day
- every day

*The real meaning of this item is often misinterpreted because the polarity of the questions and responses is reversed compared to the previous items. This item refers to "How well have you been?" Make it clear that that we are interested in the number of **good** days in an average week. We are asking for positive information, and not negative as in the previous questions. It may help to give an example (e.g., "None" means no good days in an average week, so the patient had chest trouble all the time. "Every day" means that the patient was well every day during an average week, so the patient had hardly any chest trouble at all. Check that the response to this item agrees with items 1-4. Ensure that only one answer has been marked.*

8. If you wheeze, is it worse in the morning? If you don't wheeze, go to Part 2.

_____ no
 _____ yes

*If the patient does not have a wheeze, no response will be given. Ensure that no response means no wheeze by asking the patient or by referring back to item 4. Patients should respond positively if their wheeze is worse in the morning **compared to any other time of the day or night.***

Part 2

Section 1:

How would you describe your lung/respiratory condition? Mark one answer only.

_____ The most important problem I have
 _____ Causes me a lot of problems
 _____ Causes me a few problems
 _____ Causes me no problem

This item may be further explained by "Is your lung/respiratory problem the most important problem you have in your life?" or "Do you worry about your lung/respiratory problem more than anything else?" Emphasize that "most important problem" is worse than "causes me a lot of problems." This gives some patients difficulty. Ensure that only one answer is marked.

If you have ever held a job, please mark one of these answers:

- My lung/respiratory problem made me stop my job.
- My lung/respiratory problem interferes with my job or made me change my job.
- My chest/respiratory problem does not affect my job.

If "my lung/respiratory problem made me stop my job" is checked, ensure that giving up a job permanently is what is meant. Patients often slip in a "has", so that the response means they have taken days off work or a period of time off work. Retiring early because of health problems relating to chest trouble is an appropriate reason for responding to this item. If "lung/respiratory problem interferes with my job" is marked, appropriate reasons include: having to take time off because of illness or frequent visits to the doctor, or changing jobs to one less physically demanding or less stressful. Environmental factors may instigate a job change. If the patient has never held a job, then this item is left blank. Ensure that no response means "never employed."

Section 2: These are questions about what activities usually make you feel short of breath. Mark either True or False as it applies to you **now**.

A major change in response style occurs here. Until now, patients have chosen one option from several. For most of the remaining sections, True or False must be checked for each and every item. It is worth clarifying this to the patient.

	True	False
Sitting or lying still		
Washing yourself or dressing		
Walking in the house		
Walking outside on level ground		
Walking up a flight of stairs		
Walking up hills		
Playing sports or active games (baseball, tennis, etc.)		

Most patients do not engage in physical activity. However, it must be determined whether this is a genuine lack of inclination or a limitation because of chest trouble. A response should be made if patients would like to be able to play sports and games, but cannot because of their lung/respiratory problem.

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Section 3: These are more questions about your cough and shortness of breath. Mark either True or False as it applies to you **now**.

	True	False
Coughing hurts.		
Coughing makes me tired.		
I am short of breath when I talk.		
I am short of breath when I bend over.		
My coughing or breathing disturbs my sleep.		
I become exhausted easily. <i>(e.g., doing normal daily activities such as bathing, getting dressed or housework)</i>		

Section 4: These are questions about other effects that your lung/respiratory problem may have on you. Mark either True or False as it applies to you **now**.

	True	False
My coughing or breathing is embarrassing in public.		
My lung/respiratory problem is a nuisance to my family, friends or neighbors. <i>(e.g., keeps partner or household awake with coughing, relies on friends or family for rides to the hospital or for picking up prescriptions)</i>		
I panic or get afraid when I cannot catch my breath.		
I feel that I am not in control of my lung/respiratory problem.		
I do not expect my lung/respiratory problem to get any better. <i>(i.e., than it is at the moment)</i>		
I have become frail or an invalid because of my lung/respiratory problem.		
Exercise is not safe for me. <i>(e.g., feel that exercise is not safe because of lung/respiratory problem)</i>		
Everything seems too much of an effort.		

Section 5: These are questions about your lung/respiratory medication, including oxygen, inhalers and pills. If you are not receiving medication, go to Section 6. Mark either True or False as it applies to you **now**.

	True	False
My lung/respiratory medication does not help me very much.		
I get embarrassed using my lung/respiratory medication in public.		
I have unpleasant side effects from my lung/respiratory medication. <i>(e.g., weight gain from steroids, papery skin, "shakes")</i>		
My lung/respiratory medication interferes with my life a lot. <i>(e.g., restricts mobility if on oxygen; the patient has to remember to take it with him/her at all times)</i>		

Section 6: These are questions about how your activities might be affected by your breathing problem. For each item, answer True if one or more parts applies to you because of your breathing problem. Otherwise answer False.

Emphasize to the patient that the experienced difficulties should be because of their breathing problem and not because of any other health problems or physical difficulties.

	True	False
I take a long time to get washed or dressed.		
I cannot take a bath or shower, or I take a long time to do it.		
I walk slower than other people my age, or I stop to rest.		
Jobs such as household chores take a long time, or I have to stop to rest.		
If I walk up one flight of stairs, I have to go slowly or stop.		
If I hurry or walk fast, I have to stop or slow down.		
My breathing problem makes it difficult to do things such as walking up hills, carrying things up stairs, light gardening such as weeding, dancing, playing golf or light sports such as horseshoes.		
My breathing problem makes it difficult to do things such as carrying heavy loads, digging in the garden or shoveling snow, jogging or walking briskly, playing tennis or swimming.		
My breathing problem makes it difficult to do things such as very heavy manual labor, riding a bike, running, swimming fast or playing competitive sports.		

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*These items refer to levels of activity and some patients do have difficulty with the format. The first item indicates breathlessness with a low level of physical activity; the items following this indicate breathlessness with a moderate and demanding physical activity. A patient with mild to moderate disease might answer "true" to the last two items; a patient with severe disease might answer "true" to all three items. However, some patients respond to the severity of breathlessness induced rather than the level of limitation imposed by the breathlessness. If patients do not engage in the specific activities mentioned for each item, they should select "false." Emphasize that these are examples of specific levels of activity. Patients who do not engage in demanding physical activity through choice should mark "false." Patients who would like to, but are limited by their breathlessness from participating in physical activity, should mark "true."
Check that the indicated level of limitation cross-references with the previous items in Section 6 and those in Section 2.*

Section 7: We would like to know how your breathing **usually** affects your daily life. Mark True or False as it applies to you because of **your lung/respiratory problem.**

This item can be further explained by "Does your lung/respiratory problem stop you from doing any of the following? Only respond to those items that you would like to do but your lung/respiratory problem prevents you from doing." Either "true" or "false" should be marked for each statement.

	True	False
I cannot play sports or active games.		
I cannot go out for entertainment or recreation.		
I cannot go out of the house to do the grocery shopping.		
I cannot do household chores.		
I cannot move far from my bed or chair.		

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Here is a list of other activities that your lung/respiratory problem may prevent you from doing. (You do not have to fill these in, they are just to remind you of ways in which your shortness of breath may affect you):

- Going for walks or walking the dog
- Doing activities or chores at home or in the garden
- Having sexual intercourse
- Going to church, or place of entertainment
- Going out in bad weather or into smoky rooms
- Visiting family or friends or playing with children

These are just examples and do not need to be marked.

Please write in any other important activities that your lung/respiratory problem may stop you from doing:

This section acts as a focus for the last item, so that the degree of limitation imposed on patients by their lung/respiratory problem is foremost.

Now, would you mark the one statement which you think best describes how your breathing problem affects you:

- It does not stop me from doing anything I would like to do.
- It stops me from doing one or two things I would like to do.
- It stops me from doing most of the things I would like to do.
- It stops me from doing everything I would like to do.

Check that only one answer has been marked.

Thank you for filling out this questionnaire. Please check to be sure that you have answered all questions.

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Check for missing data or any incongruous responses. In the case of the missing data, bring this to the patient's attention. There may be a valid reason for the omission or it may have been missed by mistake. Double check with the patient on any apparent inconsistencies without being critical or directive.

Thank the patients for their time and tell them how important and useful this information is to understanding how they feel about their illness and the affect it has on their day-to-day lives.

11.2. Appendix 2: Sponsor defined thresholds for laboratory values and vital signs

Sponsor-defined laboratory values of clinical concern

Parameter	Low Value of Concern	Low	High	High Value of Concern
Hemoglobin	<0.8 x LLN	[0.8 x LLN - 1 x LLN]	(1 x ULN - 1.2 x ULN]	>1.2 x ULN
Hematocrit	<0.8 x LLN	[0.8 x LLN - 1 x LLN]	(1 x ULN - 1.2 x ULN]	>1.2 x ULN
WBC	≤3.0 x 10 ⁹ /L	(3.0 x 10 ⁹ /L - 1 x LLN)	(1 x ULN - 20.0 x 10 ⁹ /L)	≥20.0 x 10 ⁹ /L
Neutrophil (total)	<0.8 x LLN	[0.8 x LLN - 1 x LLN]	(1 x ULN - 1.5 x ULN]	>1.5 x ULN
Eosinophil	ND	ND	(1 x ULN - 2 x ULN]	>2 x ULN
Platelet Count	<100 x 10 ⁹ /L	[100 x 10 ⁹ /L - 1 x LLN)	(1 x ULN - 500 x 10 ⁹ /L]	>500 x 10 ⁹ /L
AST (SGOT)	ND	ND	(1 x ULN - 2 x ULN]	>2 x ULN
ALT (SGPT)	ND	ND	(1 x ULN - 2 x ULN]	>2 x ULN
GGT	ND	ND	(1 x ULN - 2.5 x ULN]	>2.5 x ULN
Total Bilirubin	ND	ND	(1 x ULN - 1.5 x ULN]	>1.5 x ULN
Alkaline Phosphatase	ND	ND	(1 x ULN - 2 x ULN]	>2.0 x ULN
Creatinine	<0.5 x LLN	[0.5 x LLN - 1 x LLN)	(1 x ULN - 1.5 x ULN]	>1.5 x ULN
BUN (SI Units)	ND	ND	(1 x ULN - 17.85mmol/L]	>17.85mmol/L
(non SI Units)	ND	ND	(1 x ULN - 50mg/dL]	>50mg/dL
Sodium (SI Units)	≤130mmol/L	(130mmol/L - 1 x LLN)	(ULN - 150mmol/L)	≥150mmol/L
(non-SI Units)	≤130mEq/L	(130mEq/L - 1 x LLN)	(ULN - 150mEq/L)	≥150mEq/L
Potassium (SI Units)	≤3.0mmol/L	(3.0mmol/L - 1 x LLN)	(ULN - 5.5mmol/L)	≥5.5mmol/L
(non-SI Units)	≤3.0mEq/L	(3.0mEq/L - 1 x LLN)	(ULN - 5.5mEq/L)	≥5.5mEq/L
Glucose (random)	<2.0mmol/L	[2.0mmol/L - 1 x LLN)	(ULN - 8.0mmol/L]	>8.0mmol/L
Uric Acid	ND	ND	(ULN - 1.4 x ULN]	>1.4 x ULN

LLN = Lower Limit of Normal; ULN = Upper Limit of Normal; ND = Not Defined.

Note 1: (x - y) = value >x and ≤y; [x - y) = value ≥x and <y; (x - y) = value >x and <y.

Sponsor-defined criteria for evaluating vital signs

Vital Signs	Low Concern		Reference Range	High	High Concern
	Low	Low	Reference Range	High	High Concern
Systolic BP (mmHg)	<75	75-89	90-139	140-180	>180
Diastolic BP (mmHg)	<50	50-59	60-89	90-110	>110
Heart rate (bpm)	<50	50-59	60-99	100-120	>120
Orthostatic change ^a in systolic BP (mmHg)	ND	ND	ND	decrease of 10-19	decrease of ≥20
Orthostatic change ^a in diastolic BP (mmHg)	ND	ND	ND	ND	decrease of ≥10
Orthostatic change ^a in heart rate (bpm)	ND	ND	ND	ND	increase of ≥10

ND = not defined

a. Orthostatic change assessed as change between supine for 5 minutes followed by sitting with legs dependent for 1 minute.