Vascular Implications of a Naturally Occurring Asthma Exacerbation

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List of Abbreviations

ANOVA   Analysis of Variance

ACQ   Asthma Control Questionnaire

AQLQ   Asthma Quality of Life Questionnaire

CRP   C - reactive protein

CV   Cardiovascular

ED   Emergency Department

EMeRG   Emergency Medicine Research Group

EQ-5D   EuroQol 5 Dimensions

FEV_1 Forced Expiratory Volume in the first second

FMD   Flow-mediated dilation (% baseline)

FVC   Forced Vital Capacity

HR   Heart Rate

HREB   Health Research Ethics Board

IL-17   Interleukin-17

PFT   Pulmonary Function Test

PWV   Pulse wave velocity (m/s)

SSRH   Shear Stress during Reactive Hyperemia

VRH   Velocity during Reactive Hyperemia

VTI   Velocity Time Integral

Table of Contents

1   Introduction/Significance

This document is a clinical research protocol and the described study will be conducted in compliance with the protocol, Good Clinical Practices standards and associated Federal regulations (i.e. Health Canada), and all applicable institutional research requirements.

Asthma is a chronic inflammatory disease characterized by pulmonary inflammation and bronchoconstriction, with the prevalence of asthma is steadily rising worldwide[1]. **Asthma and Cardiovascular Disease:** While asthma is generally considered to be a disease of the airways, there are important systemic consequences which have predisposed people with asthma to become more likely to die from cardiovascular (CV) disease compared to non-asthmatics[2]. Additional CV risks have been reported in people with severe asthma[3], and there is a relationship between reductions in lung function and cardiac death[4]. To date, little is known in regards to the interaction between asthma exacerbations and CV risk. **Asthma and vascular dysfunction:** Brachial flow-mediated dilation (FMD) is used as a non-invasive tool to evaluate endothelial function[5]. Brachial FMD is impaired in people with coronary dysfunction[6], and can predict future CV events better than traditional CV risk factors[7]. People with asthma have previously been shown to have impaired endothelial function compared to non-asthmatics[8], but the underlying mechanism(s) are unclear. **Asthma, systemic inflammation, and CV risk:** Chronic systemic inflammation is an established risk factor and predictor of future CV events[9], and levels of systemic inflammation are increased in asthma[10,11]. Furthermore, while people with high levels of inflammation are more likely to suffer both first time and recurrent cardiac events[12,13], levels of systemic inflammation in asthma are related to disease severity and are the highest during asthma exacerbations[10,11]. Previous studies have shown that systemic inflammation directly impairs vascular function[14], and rodent work has shown that pulmonary inflammation can impair vascular function[15]. To-date, no study has examined how an asthma attack may affect vascular function and CV risk. Thus, to gain better understanding of the increased CV risks associated with asthma exacerbations, _the aim of this study is to evaluate vascular function and systemic inflammation during a naturally occurring asthma exacerbation_.

If this study finds a large systemic inflammatory insult as well as significant vascular dysfunction, as a result of an asthma exacerbation, this could have strong clinical implications. This research would highlight the importance of preventing an asthma exacerbation based on the significant negative impact that an acute exacerbation may have on the cardiovascular system. Future research on pulmonary rehabilitation for asthma could target reducing systemic inflammation and improving vascular function, as well as changes to current guidelines and recommendations for people with asthma to reflect the necessity of reducing systemic inflammation and improving vascular function to reduce CV risk.

2   Study Objectives

**Primary Objective**
To examine the endothelial function of an individual experiencing a naturally occurring asthma exacerbation.

Secondary Objective
To examine the arterial stiffness and systemic inflammation of an individual experiencing a naturally occurring asthma exacerbation.

3   Patients and Methods

3.1   Study Design

3.1.1   General Design

This study is a cohort study utilizing a repeated measure design. Asthmatic patients will be tested at 3 different time points:

- At the emergency department
- 48 hours following discharge
- 14 days following discharge

Stable asthmatic and non-asthmatic controls will be tested at two time points:

- Day 1
- 48 hours following Day 1

Vascular parameters such as flow mediated dilation (FMD; endothelial function) and pulse wave velocity (PWV; arterial stiffness) will be evaluated at each time point to assess vascular function. Blood samples will be obtained for analysis of systemic inflammatory response and immune response at each time point.

Participants will also be given Fitbit activity monitors for 7 days of monitoring, perform a full pulmonary function test (PFT) and complete 3 questionnaires; Asthma Control Questionnaire (ACQ), Asthma Quality of Life Questionnaire (AQLQ), and EQ-5D.

(A) *Cohort studies*

Definition of study groups:
Individuals experiencing an asthma exacerbation will be identified at the University of Alberta Emergency Department (ED). They will be recruited based on asthma being the primary physician diagnosis in the ED, with asthma being confirmed at a follow up visit using spirometry.

Stable asthmatic controls will be recruited from the general populations, as well as two local pulmonary clinics: The Lung Health Clinic, Edmonton, AB; and the University Lung Clinic, Edmonton, AB. These participants will be recruited if they have indicated they have been diagnosed with asthma. Both confirmed and unconfirmed asthmatics will be eligible.

Healthy controls will be recruited from the general population. They will be age-, sex, and BMI matched to the exacerbation group.

Blinding and avoiding bias:
Due to the nature of the study, blinding will not be applicable.

3.1.2 Primary Outcome Variable

Flow-mediated dilation (FMD) of the brachial artery following 5 minutes of forearm occlusion will be measured using our ultrasound machine (8L-RS 4.0-13.0 MHz probe, Vivid q, GE Healthcare, Mississauga, ON) and FMD data will be analyzed using FDA approved software available from Medical Imaging Applications (Coralville, IA, USA). FMD will be calculated as: (peak hyperemic diameter-baseline diameter)/baseline diameter x 100. Peak hyperemic brachial arterial velocity (and subsequently shear stress) will be determined using Doppler ultrasound, and used for normalization of FMD.

3.1.3 Secondary Outcome Variables

Arterial stiffness will be assessed using tonometry (Complior, Alam Medical, Saint Quentin Fallavier, France) and reported as PWV in m/s. Arterial stiffness will be determined using carotid – radial pulse wave velocity (PWV), and PWV will be calculated from measurements of pulse transit time and the distance traveled by the pulse between recording sites. Systemic inflammation and immune response will be assessed via antecubital venipuncture and analyzed at the University of Alberta. Based on prior research, important biomarkers have been identified as being involved in the inflammatory process of asthma, and are useful in identifying specific atopic phenotypes.[16] The biomarkers being analyzed will include C-reactive protein (CRP), eosinophils, neutrophils, periostin, interleukin-17 (IL-17), YKL-40, and specific immunoglobulin E (IgE).

3.2 Subject Selection and Withdrawal

3.2.1 Inclusion Criteria

To be eligible for this study, the participants have to be between the ages of 18 and 55. Asthmatics will have to present at the ED with an apparent asthma exacerbation. Stable asthma controls may have confirmed or unconfirmed asthma. Healthy control participants must be free of asthma.

3.2.2 Exclusion Criteria

Participants who at the time of the study have known heart failure or unstable cardiac disease, lung diseases other than asthma, current infections, smoking history > 10 pack years, or known metabolic conditions will be excluded from this study.

3.3 Study Procedures

Asthmatic patients will be tested at three different times:
- Day 1) ED visit
- Day 2) 48 hours post discharge
- Day 3) 14 days' post discharge

Day 1, participants will be recruited by the Emergency Medicine Research Group (EMeRG). They will receive standard emergency care for their asthma and once stabilized, informed consent will be obtained. A venous blood draw will be done prior to discharge. Once stabilized, the participant will be taken to a private area either within the ED department or Dr. Stickland's

lab in Clinical Sciences Building to ensure no interference with ED procedures. Applanation tonometry will be done to measure PWV, followed by FMD to determine endothelial function. **Day 2** the participant will return and the same assessments as Day 1 will be performed with the addition of spirometry according to standardized guidelines.[18] Medication will not be withheld prior to this assessment. A Fitbit will be given along with instructions to wear the device for 7 days.

Day 3 will consist of the same measurements done in the ED for Day 1, with the addition of 2 quality of life questionnaires, the standardized Asthma Quality of Life Questionnaire (AQLQs) and the EQ-5D (5L), and the Asthma Control Questionnaire (ACQ), finishing with a full pulmonary function test including post-bronchodilator spirometry to evaluate for airway reversibility (i.e. asthma)[19].

The participants are being tested 48 hours following the exacerbation to determine if systemic inflammation is further increased following an exacerbation, or if the exacerbation is when inflammation is at its peak. This will inform us on whether the exacerbation itself is the stimulus for increased systemic inflammation, or if it is a consequence of a stimulus in the days prior. The 14 day follow up was chosen based on the information that CRP is generally recovered to normal values after 14 days following stimulus,[20] as well, it is expected that lung function will have recovered 14 days following an exacerbation, as seen in other pulmonary disease exacerbations.[21] Day 3 will tell us what average values for the participant would most likely be and allow us to compare the values obtained from the exacerbation against a personal reference value.

Stable asthmatics and healthy control participants will be tested at two different times:
- Day 1) date that participant is available for testing
- Day 2) 48 hours after Day 1

Controls are being tested at two times to determine the degree of natural fluctuations in endothelial function, arterial stiffness, and systemic inflammation in healthy adults.

Measurements

Waist Circumference – Using a fabric tape measure, waist circumference will be measured at the level of the last rib to the nearest 0.1 cm after a normal expiration.[17] This will be used as a measure of adiposity and will potentially be used as a covariate during statistical analysis.

Arterial stiffness - Arterial stiffness will be evaluated using pulse wave velocity (PWV) between the carotid and femoral arteries. After 10 minutes of resting in a dark, quiet room in the supine position, cPWV and pPWV will be recorded using applanation tonometry (Complior, Alam Medical, Saint Quentin Fallavier, France). A series of 10 consecutive beats will be taken with a minimum quality of 85%. The distance between the carotid and femoral artery, as well as the carotid and radial artery will be recorded in mm. PWV will be measured prior to FMD and blood collection, and will be taken on all 3 days of assessments. PWV is expressed as m/s and is calculated as $PWV = L/\Delta t$, with L being the distance between the two points and Δt being the time it takes for the pulse to get from site 1 to site 2.[22]

Endothelial function - The endothelial function of the brachial artery will be evaluated after 10 minutes of rest in the supine position using ultrasound imaging (8L-RS 4.0-13.0MHz probe, Vivid q, GE Healthcare, Mississauga, ON). Baseline diameter of the brachial artery will be established, whereby the blood flow of the forearm will be occluded distal to the measuring site for the duration of 5 minutes. Upon release of the occlusion, the blood velocity and the brachial diameter will be monitored for 3 minutes, and later analyzed (Medical Imaging Applications, LLC, Coralville, IA, USA; EchoPAC PC software, version 110.x.x, GE Healthcare, Horten, Norway). Microvascular function will be evaluated as the velocity time integral-envelope of the first heartbeat of reactive hyperemia (VTI; m/s) and the velocity during reactive hyperemia (VRH) calculated as VTI x 60/HR.[23] Shear stress during reactive hyperemia (SSRH) will subsequently then be calculated as SSRH = 8 x flow / diameter and as cumulative SSRH until the time of peak FMD%.[24,25] FMD corrected for SSRH will be considered the main outcome for endothelial function in this study, and VRH and SSRH as indicators of microvascular function. Follow up tests will be conducted after a 12 hour fasting period when possible. Where applicable, the subjects will be asked to withhold any long-acting asthma medication for a minimum on 48 hours prior to the test, and short-acting asthma medications for 12 hours prior to the test.

Systemic inflammation and immune response – Serum CRP, IgE, periostin, YKL-40 and whole blood eosinophils, neutrophils, and IL-17 will be analyzed from venous blood collected at each assessment day at the end of the visit via antecubital venipuncture by a certified phlebotomist following specified guidelines.[26] With the participant sitting in a relaxed position, the upper arm will be occluded to increase the accessibility of the blood vessels. Once a vein is chosen (based on proximity to the surface, size, position and absence of scar tissue and/or pulsation), a sterile 25-gauge needle will be inserted at a 30-degree angle or less to initiate blood draw. Blood will be collected in anti-coagulant-free polypropylene tubes pre labeled with the participant's identification number, date and time, and visit number. After two tubes are collected, the tourniquet will be removed followed by the needle and pressure will be applied to the venipuncture site and held until the bleeding stops. Once collected, the blood will be left to clot for a minimum of 30 minutes followed by centrifuging at 1000g for 10 minutes at 4 degrees Celsius. The serum will be separated into aliquots of 75 µg immediately after centrifuging and then stored at -80 degrees Celsius until analysis. Analysis of inflammatory and immune markers will be completed at the University of Alberta.

Physical activity - Physical activity will be evaluated by step count using a Fitbit activity monitor (Fitbit Inc., San Francisco, CA). Participants will be instructed to wear the monitor on their wrist for 7 days, beginning the morning after Day 2 testing. It will only be removed to shower/bathe and to sleep. Total steps in each 24-hour period will be averaged and used to determine activity levels during the first week of recovery. Low active will be defined as <7,500 steps/day. Somewhat active will be defined as 7,500-9,999 steps/day. Active will be defined as > 10,000 steps/day.[27]

Pulmonary function – all participants will undergo a full pulmonary function test, according to established clinical guidelines.[19,20] The expiratory volume in 1 second (FEV_1) responses to

4x100 mg Salbutamol will be evaluated, and an increase in FEV_1 of $\geq$ 12% and 200 ml will be considered positive for significantly reversible airway constriction.[28]

Questionnaires – The participant will be asked to complete the Asthma Control Questionnaire (ACQ) to assess asthma control. The ACQ is a validated, simple 7 item questionnaire that asks questions regarding symptoms and rescue inhaler use in the last week.[29] The minimally important difference for the ACQ is 0.5 with scores ranging from 0 (totally controlled) to 6(severely uncontrolled).[30] Next the participant will be asked to fill out the standardized Asthma Quality of Life Questionnaire, which is a validated, disease specific health-related quality of life assessment that encompasses both physical and emotional impacts of asthma.[31] This questionnaire contains 32 items across 4 domains, with a minimally important difference of 0.5 with scores ranging from 1-7 with higher scores representing better quality of life.[32] Lastly, the EQ-5D (5L) will be completed by the participant to assess their generic health status and all related aspects in their quality of life.[33] The EQ-5D (5L) is a validated and reliable questionnaire consisting 5 domains, along with a visual scale to measure the participants own judgement on current health status.[34] Together, these questionnaires will give us a representations of the individuals experience with asthma, along with the physical

3.4 Statistical Plan

3.4.1 Sample Size Determination
While the impact of asthma exacerbations on vascular function is currently unknown, we based our sample size calculation on our preliminary VTI data from 11 confirmed asthmatics who underwent a mannitol airway challenge to induce airway inflammation and bronchoconstriction. Based on these data, a total of 36 asthmatics and 36 controls in each group (stable asthma, healthy) would be sufficient to detect a 13% difference between these groups in VTI. Our preliminary data show a large increase in CRP in asthmatics experiencing an exacerbation vs. stable patients (7.3 vs. 0.5 mg/L, p<0.05), which would correspond to a substantial increase in CV risk[35], and be detectable with this sample size. An additional 8 participants per group will be recruited (i.e. 44 asthmatics, 44 stable asthmatics, and 44 controls) to compensate for potential dropouts. Sub-analyses evaluating potential sex-based differences will be exploratory and results will be considered hypothesis-generating.

3.4.2 Statistical Methods
The mean differences in FMD, systemic inflammation, and arterial stiffness for ED visit compared to the control group will be evaluated using an unpaired t-test. A within-factors repeated measures analysis of variance (ANOVA) will evaluate the mean differences between each assessment day for the exacerbation group to assess change in endothelial function during exacerbation as well as the recovery period. A similar evaluation will be used for arterial stiffness and systemic inflammation/immune response. A one-way analysis of covariance (ANCOVA) will be used to correct for shear rate in FMD for all groups, with both values being reported. An α-level of 0.05 will be used as the significance level for all statistical analysis, and all results will be reported as mean $\pm$ standard deviation unless indicated otherwise.

4 Data Handling and Record Keeping

Data to be collected:

Outcome variables:

Endothelial function
Source of the data: Flow-mediated dilation test (see *measurement, endothelial function* above).
Time point for collection: Collected as the last assessment during the ED visit. For the 2 follow up visits, FMD will be done after arterial stiffness and prior to blood draw.
Who will collect the data: All data will be collected by trained research staff associated with the study.
Why the data is being collected: To evaluate the influence of acute asthma exacerbation on vascular health.
Is the data from a standardized tool: Yes.
What form will the data will take (e.g. binary, continuous (numeric), time to event): Continuous.

Arterial stiffness
Source of the data: pulse wave velocity test (see *measurements, arterial stiffness* above).
Time point for collection: At the ED, arterial stiffness will be collected after blood draw and prior to endothelial function. At the follow up visits, it will be collects as the primary assessment.
Who will collect the data: All data will be collected by trained research staff associated with the study.
Why the data is being collected: To evaluate the influence of acute asthma exacerbation on vascular health.
Is the data from a standardized tool: Yes.
What form will the data will take (e.g. binary, continuous (numeric), time to event): Continuous.

Systemic inflammation and immune response
Source of the data: Venous blood samples (see *measurements, systemic inflammation and immune response* above).
Time point for collection: At ED, blood will be collected as the primary assessment. At follow up visits, it will be collected as the final assessment.
Who will collect the data: All data will be collected by trained research staff associated with the study.
Why the data is being collected: To evaluate changes in systemic inflammatory levels and immune response throughout the study.
Is the data from a standardized tool: Yes.
What form will the data will take (e.g. binary, continuous (numeric), time to event): Continuous.

Explanatory variables and potential cofounding variables:

Participant demographics, health history, and current status
Source of the data: interview with the participant as well as medical chart and ED physician. (see appendix 5)

Time point for collection: in the ED once hemodynamically stable and while receiving treatment. At follow up visits, additional information will be collected prior to assessments.

Who will collect the data: All data will be collected by trained research staff associated with the study.

Why the data is being collected: To ensure subject meet the inclusion/exclusion requirements, to obtain information on potential confounding variables, and to obtain general sample characteristics.

Is the data from a standardized tool: No, demographics will be collected according to the data collection document provided.

What form will the data will take (e.g. binary, continuous (numeric), time to event): Nominal, continuous or ordinal.

Perceived level of control and quality of life

Source of the data: The asthma control questionnaire (see appendix 1), asthma quality of life questionnaire (see appendix 2), and EQ-5D (see appendix 3).

Time point for collection: at 14 day post-discharge follow up.

Who will collect the data: All data will be collected by trained research staff associated with the study.

Why the data is being collected: To evaluate the current levels of perceived asthma control, disease specific quality of life and generalized quality of life.

Is the data from a standardized tool: Yes.

What form will the data will take (e.g. binary, continuous (numeric), time to event): Continuous.

Lung function

Source of the data: Pulmonary function test (see *measurements, pulmonary function* above)

Time point for collection: during a pre-test session, and at each baseline time-point.

Who will collect the data: All data will be collected by trained research staff associated with the study.

Why the data is being collected: To evaluate baseline lung function at each study day.

Is the data from a standardized tool: Yes.

What form will the data will take (e.g. binary, continuous (numeric), time to event): Continuous.

Physical Activity

Source of the data: Fitbit activity monitor

Time point for collection: monitor given at end of 48 hour follow up and retrieved from participant at 14 day follow up.

Who will collect the data: All data will be collected by trained research staff associated with the study.

Why the data is being collected: To evaluate average physical activity levels.

Is the data from a standardized tool: Yes.

What form will the data will take (e.g. binary, continuous (numeric), time to event): Ordinal.

Data collection forms and questionnaires are included as appendices.

4.1 Confidentiality

Each research participant will be assigned a study ID which will not be associated with any personal identifiable information. All collected study data will be stored either on password protected computer hard drives or in locked filing cabinets.

4.2 Records Retention

All data will be stored for 5 years following the completion of the study, whereby it will be destroyed.

5 Study Auditing and Inspecting

Not applicable.

6 Budget

For complete budget, please see appendix 4.

Budget summary:

Salaries and Benefits	$14,985
Materials and Supplies	$15,098
Payment to Subjects	$10,780
Publications	$1,000
TOTAL BUDGET	**$41,863**

7 Publication Plan

Upon completion, this study is expected to be published as a peer-reviewed research article. A portion of the data from this study will be used for a MSc Thesis.

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9 Attachments

Appendix 1. Asthma Control Questionnaire (used with permission from creator).

ASTHMA CONTROL QUESTIONNAIRE (ACQ)

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DECEMBER 2002

Revised September 2010
ACQ-SA North American English Version

ASTHMA CONTROL QUESTIONNAIRE©   PATIENT ID: _____

DATE: _____

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Please answer questions 1 - 6.

Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you woken by your asthma during the night?
   - 0 Never
   - 1 Hardly ever
   - 2 A few times
   - 3 Several times
   - 4 Many times
   - 5 A great many times
   - 6 Unable to sleep because of asthma

2. On average, during the past week, how bad were your asthma symptoms when you woke up in the morning?
   - 0 No symptoms
   - 1 Very mild symptoms
   - 2 Mild symptoms
   - 3 Moderate symptoms
   - 4 Quite severe symptoms
   - 5 Severe symptoms
   - 6 Very severe symptoms

3. In general, during the past week, how limited were you in your activities because of your asthma?
   - 0 Not limited at all
   - 1 Very slightly limited
   - 2 Slightly limited
   - 3 Moderately limited
   - 4 Very limited
   - 5 Extremely limited
   - 6 Totally limited

4. In general, during the past week, how much shortness of breath did you experience because of your asthma?
   - 0 None
   - 1 A very little
   - 2 A little
   - 3 A moderate amount
   - 4 Quite a lot
   - 5 A great deal
   - 6 A very great deal

Revised September 2010
ACQ-SA North American English Version

ASTHMA CONTROL QUESTIONNAIRE©   PATIENT ID: _____

DATE: _____

Page 2 of 2

5. In general, during the past week, how much of the time did you wheeze?
   - 0 Not at all
   - 1 Hardly any of the time
   - 2 A little of the time
   - 3 A moderate amount of the time
   - 4 A lot of the time
   - 5 Most of the time
   - 6 All the time

6. On average, during the past week, how many **puffs/inhalations of short-acting bronchodilator** (eg. Ventolin/Bricanyl) have you used each day?
   (If you are not sure how to answer this question, please ask for help)
   - 0 None
   - 1 1 - 2 puffs/inhalations most days
   - 2 3 - 4 puffs/inhalations most days
   - 3 5 - 8 puffs/inhalations most days
   - 4 9 - 12 puffs/inhalations most days
   - 5 13 - 16 puffs/inhalations most days
   - 6 More than 16 puffs/inhalations most days

To be completed by a member of the clinic staff

7. FEV₁ pre-bronchodilator: ....
   FEV₁ predicted: ....
   FEV₁ %predicted: ....
   (Record actual values on the dotted lines and score the FEV₁ % predicted in the next column)
   - 0 > 95% predicted
   - 1 95 - 90%
   - 2 89 - 80%
   - 3 79 - 70%
   - 4 69 - 60%
   - 5 59 - 50%
   - 6 < 50% predicted

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Appendix 2. Asthma Quality of Life Questionnaire (used with permission from creator).

ASTHMA QUALITY OF LIFE QUESTIONNAIRE WITH STANDARDISED ACTIVITIES (AQLQ(S))

SELF-ADMINISTERED

APRIL 2008

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S)   PATIENT ID: _____

SELF-ADMINISTERED   DATE: _____

IN GENERAL, HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
7. Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7
8. Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
9. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO CIGARETTE SMOKE?	1	2	3	4	5	6	7
10. Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE?	1	2	3	4	5	6	7

HOW MUCH DISCOMFORT OR DISTRESS HAVE YOU FELT DURING THE LAST 2 WEEKS?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
12. How much discomfort or distress have you felt over the last 2 weeks as a result of COUGHING?	1	2	3	4	5	6	7

IN GENERAL, HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
13. Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
14. Experience a feeling of CHEST HEAVINESS?	1	2	3	4	5	6	7

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S)   PATIENT ID: _____

SELF-ADMINISTERED   DATE: _____

Please complete all questions by circling the number that best describes how you have been during the last 2 weeks as a result of your asthma.

HOW LIMITED HAVE YOU BEEN DURING THE LAST 2 WEEKS IN THESE ACTIVITIES AS A RESULT OF YOUR ASTHMA?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
1. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
2. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
3. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
4. WORK-RELATED ACTIVITIES (tasks you have to do at work*) *If you are not employed or self employed, these should be tasks you have to do most days.	1	2	3	4	5	6	7
5. SLEEPING	1	2	3	4	5	6	7

HOW MUCH DISCOMFORT OR DISTRESS HAVE YOU FELT DURING THE LAST 2 WEEKS?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?	1	2	3	4	5	6	7

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S)   PATIENT ID: _____

SELF-ADMINISTERED   DATE: _____

IN GENERAL, HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
15. Feel CONCERNED ABOUT THE NEED TO USE MEDICATION for your asthma?	1	2	3	4	5	6	7
16. Feel the need to CLEAR YOUR THROAT?	1	2	3	4	5	6	7
17. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO DUST?	1	2	3	4	5	6	7
18. Experience DIFFICULTY BREATHING OUT as a result of your asthma?	1	2	3	4	5	6	7
19. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF DUST?	1	2	3	4	5	6	7
20. WAKE UP IN THE MORNING WITH ASTHMA SYMPTOMS?	1	2	3	4	5	6	7
21. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
22. Feel bothered by HEAVY BREATHING?	1	2	3	4	5	6	7
23. Experience asthma symptoms as a RESULT OF THE WEATHER OR AIR POLLUTION OUTSIDE?	1	2	3	4	5	6	7
24. Were you WOKEN AT NIGHT by your asthma?	1	2	3	4	5	6	7
25. AVOID OR LIMIT GOING OUTSIDE BECAUSE OF THE WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7

Adapted from the Grand Rapids Medical Education and Research Center

IN GENERAL, HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
26. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
27. Feel AFRAID OF GETTING OUT OF BREATH?	1	2	3	4	5	6	7
28. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
29. Has your asthma INTERFERED WITH GETTING A GOOD NIGHT'S SLEEP?	1	2	3	4	5	6	7
30. Have a feeling of FIGHTING FOR AIR?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN DURING THE LAST 2 WEEKS?

	Severely Limited Most Not Done	Very Limited	Moderately Limited Several Not Done	Slightly Limited	Very Slightly Limited Very Few Not Done	Hardly Limited At All	Not Limited Have Done All Activities
31. Think of the OVERALL RANGE OF ACTIVITIES that you would have liked to have done during the last 2 weeks. How much has your range of activities been limited by your asthma?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN DURING THE LAST 2 WEEKS?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
32. Overall, among ALL THE ACTIVITIES that you have done during the last 2 weeks, how limited have you been by your asthma?	1	2	3	4	5	6	7

DOMAIN CODE:

Symptoms: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
Activity Limitation: 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
Emotional Function: 7, 13, 15, 21, 27
Environmental Stimuli: 9, 17, 23, 26

Appendix 3. EQ-5D (used with permission from creator).

EQ-5D-5L

Health Questionnaire

English version for Canada

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY
I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE
I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)
I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT
I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION
I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

The best health you can imagine
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
The worst health you can imagine

3

Appendix 4. Budget

1. Salaries and Benefits

Research Assistant: Funds are requested for the salary one research assistant (0.25 full-time equivalents, FTE). This person will assist with data collection for all aims and ensure quality control of all data collection and data analysis.

FTE	1.0	0.25
Salary (Grade 6, Step 5):	$46,155	$11,539
Benefits (23%):	$13,786	$3,447
Total Salaries and Benefits		**$14,985**

2. Material and Supply

Systemic Inflammatory Markers: Venous blood will be collected and processed for whole blood and serum analysis at each assessment for asthmatics and controls (3 assessments (asthma) X 44 participants + 2 assessments(controls) X 44 participants= 220 samples) for analysis of serum CRP, IgE, periostin, YKL-40 and whole blood eosinophils, neutrophils, and IL-17

Blood collection supplies (vacutainers, alcohol wipes, needles)	$500
Blood analysis	
	$9,698
Total Systemic Inflammatory Markers	**$10,198**

Other Supplies: A PFT will be performed on all participants to determine lung function and confirm asthma. Each PFT will cost 50$ and will be performed in all participants (n=88). Including ultrasound jelly, mouthpieces, and nose clips.

	$4,900
Total Other Supplies	**$4,900**
Total Material and Supplies	**$15,098**

3. Payment to Study Subjects

Parking and Honoraria: All research participants will be reimbursed for parking at the University of Alberta East Parkade (3 assessments (asthma) X 44 participants + 2 assessments (control) X 44 participants= 220 visits). Participants who complete all parts of the study will receive a $200 gift card (on average - $25/visit) at their choice. Honoraria for controls will be a 20$ gift card after completion of the study, and for asthma participants they will be able to keep the Fitbit used during the study valued at 125$ (20$ X 44 participants + 125$ X 44 participants).

Parking ($20/day)	$4,400
Honoraria ($200/subject)	$6,380
Total Payment to Subjects	**$10,780**

4. Publication Cost

Publications:

Paper 1	$1,000

Total Publications $1,000

<u>**5. Summary**</u>
  Salaries and Benefits $14,985
  Materials and Supplies $15,098
  Payment to Subjects $10,780
  Publications $1,000
  TOTAL BUDGET   **$41,863**

Appendix 5. Data collection sheet

Asthma Form

Collector Initials | Study ID #

Patient Information	☐ Female ☐ Male ☐ Other
	Age:_____ (years)
	Weight _____ (lbs) or _____ (kg) hint: lbs=2.2×kg
	Height _____ (ft) or _____ (inches) ex. 5 ft 8 hint: 1 foot = 12 inches
	Waist Circumference _____ (cm) Ethnicity _____

Triage Date: _____ (DD-MMM-YYYY)	Triage CTAS Score: ☐1 ☐2 ☐3 ☐4 ☐5
Triage Time: _____ (2359 HHMM)	HR _____ (bpm) BP _____ (mmHg) Temp _____ (°C) SPO₂ _____ (%)

1ˢᵗ treatment Date: ☐ Same as Triage or _____ (DD-MMM-YYYY) 1ˢᵗ treatment Time: _____ (2359 HHMM)	**Inhaled B-agonist** ☐ No ☐ Yes # of treatments **total**: _____ nebs _____ puffs (100 mcg/puff) total dose in ED care: ____.___ (mgs) (100 mcg = 0.1 mg)
1ˢᵗ treatment Date: ☐ Same as Triage or _____ (DD-MMM-YYYY) 1ˢᵗ treatment Time: _____ (2359 HHMM)	**Inhaled Anticholinergic** ☐ No ☐ Yes # of treatments **total**: _____ nebs _____ puffs (20mcg/puff) total dose in ED care: ____.___ (mgs) (20 mcg/puff= 0.02 mg)
1ˢᵗ treatment Date: ☐ Same as Triage or _____ (DD-MMM-YYYY) 1ˢᵗ treatment Time: _____ (2359 HHMM)	**Corticosteroid** ☐ No ☐ Yes (if more than one dose, check first administered) Dose: __ __ __ (mg) ☐ Prednisone ☐ Dexamethasone ☐ IV Methylprednisolone (Solu-Medrol) ☐ IV Hydrocortisone (Solu-Cortef) ☐ Other, specify:_____

Source Documentation Version Date: June 27ᵗʰ 2018

Asthma Form

Collector Initials | Study ID #

Peak Flow Measurement Date: ☐ Same as Triage or _____ (DD-MMM-YYYY) Time: _____ (2359 HHMM)	**Value:** _____ L/min (earliest recorded) **When:** (Select one) ☐ before first nebulization/MDI ☐ at triage ☐ after triage ☐ after first nebulization/MDI ☐ unknown
	Do you currently smoke? ☐ No Have you ever smoked? ☐ No ☐ Yes How long ago did you quit?/How much did you smoke? _____ ☐ Days _____ packs/day _____ ☐ Months _____ years smoking _____ ☐ Years _____ pack years (# of packs per day x # of years smoked = # pack years) ☐ Yes _____ packs/day _____ years smoking _____ pack years (# of packs per day x # of years smoked = # pack years)
Triggers	Do any of the following trigger your asthma? (check all that apply) ☐ Cats ☐ House dust mites ☐ Outdoor Environment ☐ Other animals ☐ Indoor mold ☐ Weather ☐ Perfumes ☐ Household Chemicals ☐ Work Environment ☐ ASA/NSAIDS ☐ Exercise ☐ Pollution ☐ Other: ☐ Food/Food additives ☐ Woodburning stove/fireplace ☐ Cold/Flu

Source Documentation Version Date: June 27ᵗʰ 2018

Asthma Form

Collector Initials | Study ID #

What asthma medication have you been prescribed/taken/missed in the past two weeks?
(Include medication that has been prescribed but not filled and medication missed/not taken)

Respiratory Medication	Medication currently prescribed*	Daily Dose **prescribed**	**Taking** medication as prescribed?*
Short acting beta2 agonists ☐ Ventolin ☐ Bricanyl ☐ Airomir ☐ Other:_____	☐ Yes ☐ No	☐ prn ☐ daily	☐ Yes ☐ No ☐ Missing doses ☐ Taking less/more ☐ Not prescribed
Long acting beta agonists ☐ Oxeze ☐ Serevent ☐ Onbrez ☐ Foradil ☐ Other:_____	☐ Yes ☐ No	☐ prn ☐ daily	☐ Yes ☐ No ☐ Missing doses ☐ Taking less/more ☐ Not prescribed
Inhaled corticosteroid ☐ Qvar ☐ Pulmicort ☐ Alvesco ☐ Asmanex ☐ Flovent ☐ Other:_____	☐ Yes ☐ No	Breakdown: _____ Puff(s) ☐ qday ☐ bid ☐ tid ☐ qid Daily total _____ mcg	☐ Yes ☐ No ☐ Missing doses ☐ Taking less/more ☐ Not prescribed
Combinations ☐ Symbicort ☐ Advair ☐ Zenhale ☐ Sova ☐ Combivent ☐ Other:_____	☐ Yes ☐ No	Breakdown: _____ Puff(s) ☐ qday ☐ bid ☐ tid ☐ qid Daily total _____ mcg	☐ Yes ☐ No ☐ Missing doses ☐ Taking less/more ☐ Not prescribed

*1 "Currently **prescribed**" definition: Prescribed by a healthcare professional in the last 365 days

Source Documentation Version Date: June 27ᵗʰ 2018

Asthma Form

Collector Initials | Study ID #

Respiratory Medication	Medication currently prescribed*?	Daily Dose prescribed	**Taking** medication as prescribed?
Corticosteroids ☐ Prednisone ☐ Dexamethasone ☐ Other:_____	☐ Yes ☐ No	Daily total: __ __ __ mgs ☐PO ☐IV for __ __ days	☐ Yes ☐ No ☐ Missing doses ☐ Taking less/more ☐ Not prescribed
Antibiotics Specify:_____	☐ Yes ☐ No	Breakdown: _____ mgs ☐ qday ☐ bid ☐ tid ☐ qid Daily total: __ __ __ mgs ☐PO ☐IV for __ __ days	☐ Yes ☐ No ☐ Missing doses ☐ Taking less/more ☐ Not prescribed
Inhaled anticholinergic ☐ Atrovent ☐ Spiriva ☐ Inspiolto ☐ Seebri ☐ Incruse ☐ Other:_____	☐ Yes ☐ No		☐ Yes ☐ No ☐ Missing doses ☐ Taking less/more ☐ Not prescribed
Other ☐ Xolair ☐ Singulair ☐ Nucala ☐ Accolate ☐ Other:_____	☐ Yes ☐ No		☐ Yes ☐ No ☐ Missing doses ☐ Taking less/more ☐ Not prescribed

*1 "Currently **prescribed**" definition: Prescribed by a healthcare professional in the last 365 days

Medical Intervention:

☐ IV   ☐ Chest X-RAY   ☐ Blood panel   ☐ sputum sample   ☐ other _____

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Respiratory Discharge Medication (check all that apply)	Prescription Status	Daily dose prescribed
Short acting beta2 agonists ☐ Ventolin ☐ Bovent ☐ Atrovent ☐ Other: _____	☐ Existing ☐ New	☐ prn ☐ daily
Long acting beta agonists ☐ Oxeze ☐ Serevent ☐ Onbrez ☐ Foradil ☐ Other: _____	☐ Existing ☐ New	☐ prn ☐ daily
Inhaled corticosteroid ☐ Qvar ☐ Pulmicort ☐ Alvesco ☐ Flovent ☐ Other: _____	☐ Existing ☐ New	Breakdown: _____ Puff(s) ☐ qday ☐ bid ☐ tid ☐ qid Daily total _____ mcg
Combinations ☐ Symbicort ☐ Advair ☐ Zenhale ☐ Breo ☐ Combivent ☐ Other: _____	☐ Existing ☐ New	Breakdown: _____ Puff(s) ☐ qday ☐ bid ☐ tid ☐ qid Daily total _____ mcg
Corticosteroids ☐ Prednisone ☐ Dexamethasone ☐ Other: _____	☐ Existing ☐ New	Daily total: ___ ___ ___ mgs ☐ PO ☐ IV for ___ ___ days

Source Documentation Version Date: June 27th 2018

Antibiotics Specify: _____	☐ Existing ☐ New	Breakdown: _____ mgs ☐ qday ☐ bid ☐ tid ☐ qid Daily total: ___ ___ ___ mgs ☐ PO ☐ IV for ___ ___ days
Inhaled anticholinergic ☐ Atrovent ☐ Spiriva ☐ Tudorza ☐ Seebri ☐ Incruse ☐ Other: _____	☐ Existing ☐ New	
Other ☐ Zenhale ☐ Uniphyl ☐ Singulair ☐ Accolate ☐ Other: _____	☐ Existing ☐ New	

Other medication use (including vitamins, supplements, and non-prescription i.e. aspirin):
_____
_____

Vaccination within the past month?   YES   NO

Type: _____   UNKNOWN

Menstrual status:

Contraceptives:	N/A	YES	NO	Type: _____
Post-menopausal:	N/A	YES	NO	Year: _____

If NO: Date of first day of your last period: _____

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Medical history:

Asthma:	YES	NO	Age/Date of Diagnosis _____
Other lung disease:	YES	NO	
Heart condition:	YES	NO	
Current infections:	YES	NO	

Other know conditions:
_____
_____

Exacerbation History:

Number of exacerbations requiring ED care in past 12 months: _____
Date of most recent exacerbation: _____

Allergies: YES   NO
If YES, please list all allergies:
_____
_____

Current Status Within past 12 hours

Alcohol:	YES	NO	Time: _____ Amount: _____
Smoking:	YES	NO	Time: _____ Amount: _____
Exercise:	YES	NO	Time: _____ Amount: _____
Coffee/Tea:	YES	NO	Time: _____ Amount: _____
Food:	YES	NO	Time: _____ Type: _____

Asthma Action Plan reviewed?   YES   NO

Additional notes/comments:
_____
_____
_____
_____
_____

Data collection completed by: _____

Source Documentation Version Date: June 27th 2018