Vascular Implications of a Naturally Occurring Asthma Exacerbation

Authors: Dr. Michael Stickland, PhD¹; Shelby Henry, BKin².

Institutions:
¹Department of Medicine, Faculty of Medicine and Dentistry
²Faculty of Rehabilitation Medicine

Corresponding Author:
Dr. Michael Stickland, PhD
Department of Medicine
3-135 Clinical Sciences Building
University of Alberta
Edmonton, Alberta
Canada
T6G 2J3
Ph. 780-492-3995
Fax. 780-492-4483
Email: michael.stickland@ualberta.ca

Protocol/version #: Pro00083372
Current Version Date: Sept 14, 2018
Previous IRB Approved Version
Dates: n/a

CONFIDENTIAL
This document is confidential and the property of individual. No part of it may be transmitted, reproduced, published, or used by other persons without prior written authorization from the author.

Adapted from the Grand Rapids Medical Education and Research Center
**List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>ACQ</td>
<td>Asthma Control Questionnaire</td>
</tr>
<tr>
<td>AQLQ</td>
<td>Asthma Quality of Life Questionnaire</td>
</tr>
<tr>
<td>CRP</td>
<td>C - reactive protein</td>
</tr>
<tr>
<td>CV</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency Department</td>
</tr>
<tr>
<td>EMeRG</td>
<td>Emergency Medicine Research Group</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>EuroQol 5 Dimensions</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>Forced Expiratory Volume in the first second</td>
</tr>
<tr>
<td>FMD</td>
<td>Flow-mediated dilation (% baseline)</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced Vital Capacity</td>
</tr>
<tr>
<td>HR</td>
<td>Heart Rate</td>
</tr>
<tr>
<td>HREB</td>
<td>Health Research Ethics Board</td>
</tr>
<tr>
<td>IL-17</td>
<td>Interleukin-17</td>
</tr>
<tr>
<td>PFT</td>
<td>Pulmonary Function Test</td>
</tr>
<tr>
<td>PWV</td>
<td>Pulse wave velocity (m/s)</td>
</tr>
<tr>
<td>SSRH</td>
<td>Shear Stress during Reactive Hyperemia</td>
</tr>
<tr>
<td>VRH</td>
<td>Velocity during Reactive Hyperemia</td>
</tr>
<tr>
<td>VTI</td>
<td>Velocity Time Integral</td>
</tr>
</tbody>
</table>
# Table of Contents

1 INTRODUCTION/SIGNIFICANCE ................................................................................................................. 4
2 STUDY OBJECTIVES ................................................................................................................................. 4
3 PATIENTS AND METHODS ....................................................................................................................... 5
   3.1 STUDY DESIGN ................................................................................................................................. 5
   3.1.1 General Design ........................................................................................................................... 5
   3.1.2 Primary Outcome Variable ......................................................................................................... 5
   3.1.3 Secondary Outcome Variables ................................................................................................... 6
   3.2 SUBJECT SELECTION AND WITHDRAWAL ................................................................................. 6
   3.2.1 Inclusion Criteria ......................................................................................................................... 6
   3.2.2 Exclusion Criteria ....................................................................................................................... 6
   3.3 STUDY PROCEDURES ....................................................................................................................... 6
   3.4 STATISTICAL PLAN .......................................................................................................................... 9
   3.4.1 Sample Size Determination ....................................................................................................... 9
   3.4.2 Statistical Methods ...................................................................................................................... 9
4 DATA HANDLING AND RECORD KEEPING ...................................................................................... 9
   4.1 CONFIDENTIALITY .......................................................................................................................... 12
   4.2 RECORDS RETENTION ............................................................................................................... 12
5 STUDY AUDITING AND INSPECTING ............................................................................................... 12
6 BUDGET .................................................................................................................................................. 12
7 PUBLICATION PLAN ............................................................................................................................. 12
8 REFERENCES ............................................................................................................................................ 12
9 ATTACHMENTS ....................................................................................................................................... 15
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

Non-asthmatic controls will be tested at two time points:

- Day 1
- 14 days later

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.

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. 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 65, have a body mass index of less than 35 kg/m². Asthmatics will have to present at the ED with an apparent asthma exacerbation. Control subjects 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 waist circumference >88 cm for women and >102 cm for men, indicating increased risk of metabolic issues will be excluded from the 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. 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)\(^9\).

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.

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 in which the participants that are at an increased risk of metabolic problems will be excluded.

**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 $PWV = \frac{L}{\Delta t}$, with $L$ being the distance between the two points and $\Delta t$ 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. Shear stress during reactive hyperemia (SSRH) will subsequently be calculated as SSRH = 8 x flow / diameter and as cumulative SSRH until the time of peak FMD%. 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. 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.

**Pulmonary function** – all participants will undergo a full pulmonary function test, according to established clinical guidelines. The expiratory volume in 1 second (FEV1) responses to 4x100 mg Salbutamol will be evaluated, and an increase in FEV1 of ≥ 12% and 200 ml will be considered positive for significantly reversible airway constriction.
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. The minimally important difference for the ACQ is 0.5 with scores ranging from 0 (totally controlled) to 6 (severely uncontrolled). 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. 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. 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. 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. 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 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, and be detectable with this sample size. An additional 8 participants per group will be recruited (i.e. 44 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 ± 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 collected 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:

<table>
<thead>
<tr>
<th>Item</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salaries and Benefits</td>
<td>$14,985</td>
</tr>
<tr>
<td>Materials and Supplies</td>
<td>$15,098</td>
</tr>
<tr>
<td>Payment to Subjects</td>
<td>$10,780</td>
</tr>
<tr>
<td>Publications</td>
<td>$1,000</td>
</tr>
<tr>
<td><strong>TOTAL BUDGET</strong></td>
<td><strong>$41,863</strong></td>
</tr>
</tbody>
</table>

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.

8 References


9 Attachments

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

---

ASTHMA CONTROL QUESTIONNAIRE (ACQ)

---

ASTHMA CONTROL QUESTIONNAIRE

---

To be completed by a member of the clinic staff

---

FEV1 Reference values

---

---

---

---

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

**Asthma Quality of Life Questionnaire with Standardised Activities (AQoL-QS)**

**SELF-ADMINISTERED**

<table>
<thead>
<tr>
<th><strong>Asthma Quality of Life Questionnaire (SQ)</strong></th>
<th><strong>Patient ID: ____________________</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date: ____________________</strong></td>
<td><strong>Page 1 of 2</strong></td>
</tr>
</tbody>
</table>

**In general, how much of the time during the last 2 weeks did you:**

1. Feel **CONCERNED ABOUT HAVING ASTHMA**?
   - **Very Often**
   - **Often**
   - **Sometimes**
   - **Rarely**
   - **Never**

2. Feel **SHORT OF BREATH** as a result of your asthma?
   - **Very Often**
   - **Often**
   - **Sometimes**
   - **Rarely**
   - **Never**

3. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO CIGARETTE SMOKE?
   - **Very Often**
   - **Often**
   - **Sometimes**
   - **Rarely**
   - **Never**

4. Experience a **WHEEZE in your chest**?
   - **Very Often**
   - **Often**
   - **Sometimes**
   - **Rarely**
   - **Never**

5. Feel you had to **AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE**?
   - **Very Often**
   - **Often**
   - **Sometimes**
   - **Rarely**
   - **Never**

6. How much discomfort or distress have you felt during the last 2 weeks?
   - **Very Often**
   - **Often**
   - **Sometimes**
   - **Rarely**
   - **Never**

7. **Frustrated** as a result of your asthma?
   - **Very Often**
   - **Often**
   - **Sometimes**
   - **Rarely**
   - **Never**

8. Experience a feeling of **CHEST HEAVINESS**?
   - **Very Often**
   - **Often**
   - **Sometimes**
   - **Rarely**
   - **Never**

9. **How limited have you been during the last 2 weeks in these activities as a result of your asthma?**

   - **Very Limited**
   - **Extremely Limited**
   - **Very Limited**
   - **Somewhat Limited**
   - **A Little Limited**
   - **Not at all Limited**

10. **Moderate Activities** (such as yard work, gardening, shopping, climbing stairs)
    - **Very Limited**
    - **Extremely Limited**
    - **Very Limited**
    - **Somewhat Limited**
    - **A Little Limited**
    - **Not at all Limited**

11. **Social Activities** (such as visiting friends or relatives)
    - **Very Limited**
    - **Extremely Limited**
    - **Very Limited**
    - **Somewhat Limited**
    - **A Little Limited**
    - **Not at all Limited**

12. **Work-Related Activities** (such as working in a factory)
    - **Very Limited**
    - **Extremely Limited**
    - **Very Limited**
    - **Somewhat Limited**
    - **A Little Limited**
    - **Not at all Limited**

13. **Sleeping**
    - **Very Limited**
    - **Extremely Limited**
    - **Very Limited**
    - **Somewhat Limited**
    - **A Little Limited**
    - **Not at all Limited**

**How much discomfort or distress have you felt during the last 2 weeks?**

- **Very Well**
- **A Great Deal**
- **A Great Deal**
- **Some**
- **A Little**
- **Very Poor**

**Asthma Quality of Life Questionnaire (SQ)**

**SELF-ADMINISTERED**

<table>
<thead>
<tr>
<th><strong>Asthma Quality of Life Questionnaire (SQ)</strong></th>
<th><strong>Patient ID: ____________________</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date: ____________________</strong></td>
<td><strong>Page 2 of 2</strong></td>
</tr>
</tbody>
</table>

**How much discomfort or distress have you felt during the last 2 weeks?**

1. **Feeling **CONCERNED ABOUT HAVING ASTHMA**?
   - **Very Often**
   - **Often**
   - **Sometimes**
   - **Rarely**
   - **Never**

2. Feel **SHORT OF BREATH** as a result of your asthma?
   - **Very Often**
   - **Often**
   - **Sometimes**
   - **Rarely**
   - **Never**

3. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO CIGARETTE SMOKE?
   - **Very Often**
   - **Often**
   - **Sometimes**
   - **Rarely**
   - **Never**

4. Experience a **WHEEZE in your chest**?
   - **Very Often**
   - **Often**
   - **Sometimes**
   - **Rarely**
   - **Never**

5. Feel you had to **AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE**?
   - **Very Often**
   - **Often**
   - **Sometimes**
   - **Rarely**
   - **Never**

6. How much discomfort or distress have you felt during the last 2 weeks as a result of **CHEST TIGHTNESS**?
   - **Very Often**
   - **Often**
   - **Sometimes**
   - **Rarely**
   - **Never**

7. **Frustrated** as a result of your asthma?
   - **Very Often**
   - **Often**
   - **Sometimes**
   - **Rarely**
   - **Never**

8. Experience a feeling of **CHEST HEAVINESS**?
   - **Very Often**
   - **Often**
   - **Sometimes**
   - **Rarely**
   - **Never**

9. **How limited have you been during the last 2 weeks in these activities as a result of your asthma?**

   - **Very Limited**
   - **Extremely Limited**
   - **Very Limited**
   - **Somewhat Limited**
   - **A Little Limited**
   - **Not at all Limited**

10. **Moderate Activities** (such as yard work, gardening, shopping, climbing stairs)
    - **Very Limited**
    - **Extremely Limited**
    - **Very Limited**
    - **Somewhat Limited**
    - **A Little Limited**
    - **Not at all Limited**

11. **Social Activities** (such as visiting friends or relatives)
    - **Very Limited**
    - **Extremely Limited**
    - **Very Limited**
    - **Somewhat Limited**
    - **A Little Limited**
    - **Not at all Limited**

12. **Work-Related Activities** (such as working in a factory)
    - **Very Limited**
    - **Extremely Limited**
    - **Very Limited**
    - **Somewhat Limited**
    - **A Little Limited**
    - **Not at all Limited**

13. **Sleeping**
    - **Very Limited**
    - **Extremely Limited**
    - **Very Limited**
    - **Somewhat Limited**
    - **A Little Limited**
    - **Not at all Limited**

**How much discomfort or distress have you felt during the last 2 weeks?**

- **Very Well**
- **A Great Deal**
- **A Great Deal**
- **Some**
- **A Little**
- **Very Poor**
### Asthma Quality of Life Questionnaire (S)

**Patent ID:**

**Self-Administered**

**Date:**

**Page 1 of 1**

#### In general, how much of the time during the last 2 weeks did you:

<table>
<thead>
<tr>
<th>Activity</th>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>26. Experience asthma symptoms as a result of being exposed to strong smells or perfume?</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27. Feel afraid of getting out of breath?</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28. Feel you had to avoid a situation or environment because of strong smells or perfume?</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29. Have your asthma interfered with getting a good night's sleep?</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30. Have a feeling of fighting for air?</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### How limited have you been during the last 2 weeks?

<table>
<thead>
<tr>
<th>Severity</th>
<th>Limited All the Time</th>
<th>Very Limited</th>
<th>Moderate Limitation</th>
<th>Some Limitation</th>
<th>A Little Limitation</th>
<th>No Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>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?</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### How limited have you been during the last 2 weeks?

<table>
<thead>
<tr>
<th>Limitation</th>
<th>Totally Limited</th>
<th>Extremely Limited</th>
<th>Very Limited</th>
<th>Moderate Limitation</th>
<th>Some Limitation</th>
<th>A Little Limitation</th>
<th>No Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>32. Overall, among all the activities that you have done during the last 2 weeks, how limited have you been by your asthma?</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Domain Code:**

- **Symptoms:** 6, 9, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
- **Activity Limitation:** 1, 2, 3, 4, 5, 11, 15, 18, 20, 21, 23
- **Emotional Function:** 7, 13, 16, 21, 27
- **Environmental Stress:** 8, 17, 25, 36
Appendix 3. EQ-5D (used with permission from creator).
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.

<table>
<thead>
<tr>
<th>FTE</th>
<th>Salary (Grade 6, Step 5): $46,155</th>
<th>Benefits (23%): $13,786</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$14,985</td>
<td>$14,985</td>
</tr>
</tbody>
</table>

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.

Parking ($20/day): $4,400
Honoraria ($200/subject): $6,380

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
5. Summary

Total Publications $1,000

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salaries and Benefits</td>
<td>$14,985</td>
</tr>
<tr>
<td>Materials and Supplies</td>
<td>$15,098</td>
</tr>
<tr>
<td>Payment to Subjects</td>
<td>$10,780</td>
</tr>
<tr>
<td>Publications</td>
<td>$1,000</td>
</tr>
<tr>
<td><strong>TOTAL BUDGET</strong></td>
<td><strong>$41,863</strong></td>
</tr>
</tbody>
</table>
Appendix 5. Data collection sheet