IRB-HSR PROTOCOL

Investigator Agreement

BY SIGNING THIS DOCUMENT, THE INVESTIGATOR CONFIRMS:

1. I am not currently debarred by the US FDA from involvement in clinical research studies.
2. I am not involved in any regulatory or misconduct litigation or investigation by the FDA.
3. That if this study involves any funding or resources from an outside source, or if you will be sharing data outside of UVA prior to publication that you will contact the Dean's office regarding the need for a contract and letter of indemnification. If it is determined that either a contract or letter of indemnification is needed, subjects cannot be enrolled until these documents are complete.
4. The proposed research project will be conducted by me or under my close supervision. It will be conducted in accordance with the protocol submitted to and approved by the IRB including any modifications, amendments or addendums submitted and approved by the IRB throughout the life of the protocol.
5. That no personnel will be allowed to work on this protocol until they have completed the IRB-HSR On-line training and the IRB-HSR has been notified.
6. That all personnel working on this protocol will follow all IRB-HSR Policies and Procedures as stated on the IRB-HSR Website http://www.virginia.edu/vprgs/irb/ and on the School of Medicine Clinical Trials Office Website: http://knowledgelink.healthsystem.virginia.edu/intranet/hes/cto/sops/sop_index.cfm
7. I will ensure that all those delegated tasks relating to this study, whether explicitly or implicitly, are capable through expertise, training , experience or credentialing to undertake those tasks.
8. I confirm that the implications of the study have been discussed with all Departments that might be affected by it and have obtained their agreement for the study to take place.
9. That no subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment
10. That any materials used to recruit subjects will be approved by the IRB-HSR prior to use.
11. That all subjects will sign a copy of the most current consent form that has a non-expired IRB-HSR approval stamp.
12. That any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.
13. Any significant findings that become known in the course of the research that might affect the willingness of subjects to enroll or to continue to take part, will be promptly reported to the IRB.
14. I will report immediately to the IRB any unanticipated problems involving risk to subjects or to others including adverse reactions to biologics, drugs or medical devices.
15. That any serious deviation from the protocol will be reported promptly to the Board in writing.
16. That any data breach will be reported to the IRB, the UVa Corporate Compliance and Privacy Office , UVa Police as applicable.
17. That the continuation status report for this protocol will be completed and returned within the time limit stated on the form.
18. That the IRB-HSR office will be notified within 30 days of a change in the Principal Investigator or of the closure of this study.
19. That a new PI will be assigned if the current PI will not be at UVA for an extended period of time.
20. Signed consent forms and other research records will be retained in a confidential manner. Records will be kept at least 6 years after completion of the study. These are considered institutional records and may not be

transferred to another institution. A copy of the documents may be taken with the Principal investigator when transferring to another institution.

The IRB reserves the right to terminate this study at any time if, in its opinion, (1) the risks of further experimentation are prohibitive, or (2) the above agreement is breached.

Investigators Experience

Dr Heymann is a Professor in the Department of Pediatrics- Allergy and Pulmonary Division. He has been at the University of Virginia for 33 years and has over 27 years of experience in allergy pulmonary research.

Signatures

Principal Investigator

_____	_____	_____
Principal Investigator Signature	Principal Investigator Name Printed	Date

Department Chair

BY SIGNING THIS DOCUMENT THE DEPARTMENT CHAIR AGREES:

1. To work with the investigator and with the board as needed, to maintain compliance with this agreement.
2. That the Principal Investigator is qualified to perform this study.
3. That the protocol is scientifically relevant and sound.

_____	_____	_____
Department Chair or Designee Signature	Department Chair or Designee Name Printed	Date

The person signing as the Department Chair cannot be the Principal Investigator or a sub-investigator on this protocol.
The Department Chair or Designee signature is ONLY required if this is a new protocol or a modification changing the Principal Investigator

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Study Synopsis

Protocol for "Evaluating the Asthmatic Response to an Experimental Infection with Rhinovirus in the Atopic Host" (U01-UVA-03; IRB HSR# 12673)

Title	Evaluating the Asthmatic Response to an Experimental Infection with Rhinovirus in the Atopic Host
Short Title	Evaluating the Asthmatic Response to an Experimental Infection with RV-16
Rationale	Most studies of viral infections in asthma are cross-sectional, or prospective studies in design and have been devoted to the evaluation of subjects when they are experiencing acute symptoms. These study designs obviate chances to evaluate 1) asthma control before the attack occurs, and 2) early, innate, events which occur from the time of virus exposure (or inoculation) to peak symptoms which can have important mechanistic and prevention implications. Using the experimental RV challenge model, we have the opportunity to evaluate the status of asthmatic subjects and identify pre-existing risk factors (e.g., airway inflammation) during a run-in period before virus inoculation that may play a central role in the development of asthma symptoms provoked by RV. Additionally, the subjects in our challenge studies are monitored frequently (at least daily) over the first four days of the infection, which provides important time-sequence information to improve our understanding for mechanisms in the pathogenesis of the asthmatic response to RV.
Clinical Phase	Phase II
Mechanistic Study	×*Yes* □*No*
IND Sponsor	Ronald B. Turner, MD (IND# 15162)
Principal Investigators	Thomas Platts-Mills, MD, PhD, FRS and Peter W. Heymann, MD
Participating Site(s)	University of Virginia (Charlottesville, VA)
Accrual Objective	36 total subjects: 18 atopic asthmatics and 18 non-asthmatic, non-allergic controls
Study Objective	Using rhinovirus strain 16 (RV-16) for inoculation, this study is designed to examine mechanisms of the asthmatic response to RV in the atopic host. In keeping with this, the primary objective of this investigation will be to test the hypothesis that mild asthmatics enrolled in this study will experience significantly increased lower respiratory tract symptoms over the first 4 days after experimental inoculation with RV-16 than non-allergic, non-asthmatic controls (as shown in our previous studies), and further demonstrate in mechanistic studies that this increase is due to amplified allergic pathways that will serve to guide the development of new treatments to prevent asthma attacks provoked by RV.
Study Design	This will be a 5 week longitudinal study of 18 young allergic adults with mild asthma and 18 non-asthmatic controls who will be evaluated for 1 week to establish baseline symptoms and lung function, followed by an inoculation with GMP RV-16 and subsequent clinical and laboratory (mechanistic) monitoring for an additional 4 weeks.
Study Duration	60 months

Primary Endpoint	The primary endpoint will be based on the comparison of cumulative lower respiratory tract symptom scores (CLRTS) in the asthmatic subjects compared to the non-asthmatic subjects over the first 4 days of acute infection. Diary cards will be scored daily for cough, shortness of breath, chest discomfort and wheezing using a modification of the Jackson criteria as previously described (16).
Secondary Endpoints	Secondary outcomes will include comparisons of viral replication and clearance; measurements of eNO; selected cytokines, chemokines, and mediators in nasal wash and nasal lining fluid; weights of nasal mucous and secretions collected during the first 4 days of the infection; eosinophil and neutrophil counts in nasal washes, and circulating (blood) eosniophils and regulatory/effector T-cells; and finally gene expression analyses in Rhinoprobe scrapings of the nasal epithelium from asthmatic and control subjects. Data for secondary outcome variables will be collected at baseline, and then again on post-challenge days 1, 2, 3, and 4, and on follow-up days 7, 10, 14, and 21. Many of these secondary outcomes will be analyzed by way of repeated measures ANOVA in exactly the same manner as in our previous experimental rhinovirus challenge study (8), a study in which the same rhinovirus-challenge design and strain of rhinovirus (RV-16) was used.
Inclusion Criteria	**ALL SUBJECTS:** • Subjects must be able to understand and provide written informed consent • Age 18 to ≤ 40 years of age, any gender, any racial/ethnic origin. • Participant must be willing to comply with study procedures and requirements. Participant must be considered eligible for participation based on results of screening procedures conducted by protocol number 20100686 at VCU and IRB# 12656 at UVA. **Subjects with asthma** Criteria for inclusion will include those: • with physician-diagnosed, mild asthma who are only using bronchodilators (e.g. albuterol) for symptom control. • Asthma Control Test (ACT) Questionnaire Score a > 19 at enrollment before the inoculation with RV-16 (See Appendix: Asthma Control Test). • Short-acting beta-agonist use < daily in last 4 weeks • FEV1 > 70%, or FEV1/FVC ratio > 75% for subjects with FVC values between 80 and 87% predicted whose FEV1 values fall below 70%. a positive methacholine challenge test (i.e. at least a 20% fall in FEV_1) at a methacholine concentration of 16 mg/ml or less (15). The methacholine test will not be done if subjects have used albuterol within 4 hours of the test procedure.Evidence for atopy demonstrated during screening (under IRB protocol# 12656) as judged by positive prick skin tests to one or more aero-allergens. • **Control subjects.** Criteria for inclusion will include those who do not have a history of asthma or allergic disorders (e.g. allergic rhinitis, atopic dermatitis, or food allergies).
Exclusion Criteria	**ALL SUBJECTS:** • Inability or unwillingness of a participant *or subject's legal representative* to give written informed consent *and HIPPA authorization* • Positive test for serum neutralizing antibody to RV-16. Subjects with a neutralizing antibody titer ≥ 1:4 will be excluded. • Chronic heart disease, lung diseases other than asthma, or other chronic illnesses, including primary and/or secondary immunodeficiency. • An upper or lower respiratory tract infection within six weeks prior to enrollment

	• Who have required nasal or sinus surgery, excluding surgery for a deviated septum within 12 months prior to enrollment. • Who have a 5 pack/year history of smoking, or any smoking within the last 6 months. • Female subjects who are or who plan to become pregnant during the study, or who are nursing a baby. Additionally, to be included in this study, a woman of child-bearing potential must have a negative urine pregnancy test at screening, during the run-in, and prior to viral inoculation and agree to use an effective method of birth control such as, but not limited to, birth control pills, contraceptive foam, diaphragm, IUD, abstinence, or condoms. • Absolute neutrophil count (ANC) < 1500 cells/mm3 (or 1.5 K/uL) detected during screening within 6 weeks of enrollment. • **Subjects with asthma** **Criteria for exclusion will include those:** • Who have required inhaled steroids (used for asthma), nasal steroids (used for allergic rhinitis), cromolyn, nedocromil sodium, ipratropium bromide, or leukotriene modifiers during the month prior to enrollment, oral steroids within 6 weeks of enrollment, omalizumab (Xolair®) within 6 months prior to enrollment, or who are currently using beta adrenergic blocking agents. • Who have been hospitalized or treated in the emergency room (unless the treatment involved the use of a bronchodilator only) for asthma within the last three years. • To avoid RV-16 inoculations in subjects with more restrictive lung volumes, those whose FVC is < 80% predicted will be excluded. Subjects who are currently receiving allergen immunotherapy (IT), or who have received allergen IT within the last 3 years. Subjects who have had one or more night time awakenings caused by asthma symptoms and/or who have needed their SABA (albuterol) inhaler for asthma symptoms ≥ 4 days during the week before enrollment, or during the week before the inoculation with RV-16. **Control subjects** • Who have a positive methacholine test, or positive prick skin tests at screening under IRB protocol # 12656.
Investigational Product(s)/Intervention(s)	All subjects will receive Rhinovirus 16 challenge IND# 15162

Study Procedures	The following procedures will be performed in this sub-study: • Medical and allergy history • Limited physical exam • Urine pregnancy test/Urine LTE4 • Nasal wash • Monitoring of nasal mucous and secretion weights during the first 4 days of the infection • Skin testing, including tests for Alternaria, dust mite, and ragweed, grass and tree pollen allergens • Spirometry • Exhaled Nitric Oxide

	• CBC/differential • Serum IgE levels (total and allergen specific) • T-cells blood test • RV 16 antibody titers by neutralization assay • Methacholine challenge • Impulse oscillometry • RV 16 inoculation • Completion of diary cards • Added to this study will be a nasal specimen obtained by using an ASI Rhino-Pro® nasal mucosal curette to do a light scraping along the inferior turbinate of each nostril to collect epithelial cells at 4 time points during the study. • A small piece of gauze (Surgicel®) will be applied to the inferior turbinate of each nostril at 3 different time points during the study to sample nasal lining fluid to measure albumin, mediators and cytokines.
Statistical considerations	Using Monte Carlo simulation to estimate statistical power, 36 subjects will be enrolled. For 1 week prior to inoculation with RV-16 and over the period of 28 days after the infection subjects will be monitored and evaluated. Accounting for a 20% drop out rate or failure to develop a cold, 14 subjects in each treatment arm are expected to complete the study. Based on power calculations, this will be sufficient to detect a 3.8 unit difference in the CLTRS score during the first 4 days after RV inoculation between the 2 groups. The power of the test was determined to be > 0.85. Statistical analyses of the data will use methods published in our previous experimental challenges of asthmatic and non-asthmatic subjects challenged with RV-16 (16).

Brief Summary/Abstract

This investigation will provide a time-sequence analysis of the response to rhinovirus following viral inoculation in asthmatic subjects who are sero-negative to the strain of rhinovirus causing the infection. The strain of rhinovirus that will be used in this study is a pool of rhinovirus (strain 16) that will be provided by Dr. Ronald Turner at the University of Virginia. Dr. Turner is a co-investigator in this proposal and has collaborated with Johnson and Johnson to produce a rhinovirus pool under GMP conditions. This pool has already been safety tested by Dr. Turner and has recently been approved for experimental challenge studies by the FDA (BB-IND # 15162). In clinical trials, 52 non-allergic subjects have been inoculated by Dr. Turner with the pool of RV-16 at the University of Virginia. The upper respiratory tract symptom scores using the Jackson criteria for scoring cold symptoms (reference #'s 11 and 12), were very similar to symptom scores recorded by subjects in previous investigations using rhinovirus 16 (RV-16), prior to the requirement that these pools must be produced under GMP conditions (8). Before the requirement for using GMP produced pools of rhinovirus for experimental challenges, several publications, including our own [IRB # 7231: "Experimental Human Rhinovirus Infections in Patients with Asthma"], have demonstrated the safety of using RV-16 for experimental infections in asthmatic subjects (8, 17-19).

Background

Among school-age children with asthma, a large percentage (80%) are atopic. In addition, population surveys have shown a positive correlation between increased levels of total serum IgE, bronchial hyperreactivity, and the risks of having asthma among children and adults (1,2). However, it is also clear that exacerbations of asthma are often triggered by viral respiratory tract infections, especially infections with human rhinovirus (3-5). Several studies, including our own, have demonstrated an enhancement of bronchial hyperreactivity during rhinovirus colds in atopic individuals (6-8). Moreover, our cross-sectional studies of children and young adults who were evaluated in the emergency room (ER), or hospital, for exacerbations of asthma have shown that the majority (80 to 90%) of those who are infected with rhinovirus are also atopic (4, 9).

Using the experimental rhinovirus challenge model developed at the University of Virginia, we have evaluated 16 young adults with mild asthma and 9 non-allergic subjects without asthma during an experimental infection with rhinovirus [strain 16] (8). The results showed that upper respiratory tract symptom scores among the asthmatics were prolonged compared to controls. In addition, 6 of the asthmatics who had substantially elevated levels of total serum IgE (371-820 IU/ml) showed greater sensitivity to methacholine and had significantly higher levels of expired nitric oxide (FeNO), a marker of lower airway inflammation, before and during the infection. Moreover, the asthmatics with high levels of total IgE (compared to those with lower IgE levels) also had increased blood eosinophil counts, along with higher levels of eosinophilic cationic protein (ECP) in their nasal washes reflecting inflammation in the upper airway. Taken together, these data suggest that patients with allergic asthma and high levels of total IgE are more likely to have inflammation in their airways, together with an augmented eosinophil response, before virus inoculation and during the infection. This suggests that the persistance of inflammation in the airway of asthmatics who are highly allergic may play a central role in the pathogenesis of asthma exacerbations caused by rhinovirus. If so, then it may be more important to develop treatments designed to reduce allergen-induced airway inflammation than to develop anti-viral therapies focused on RV. As a result, this research will continue to examine mechanisms of the asthmatic response to RV in the atopic host. As new methods and tests become available to examine mechanisms, this protocol is designed to use our on-going study design for experimental RV challenges and to add exploratory methods and procedures that have are known to have a proven safety profile. This is being done to learn new information and to improve our methods of evaluation. Because this is a labor intensive protocol and because the inclusion and exclusion criteria for enrollment obviate studies involving a large number of subjects, it is not feasible to study each new test and procedure in a large number of subjects. However, as results become available, we can use the preliminary data to do power analyses and determine the number of subjects and samples needed to test new hypotheses. As a result, we are likely to increase the number of subjects planned for this on-going research and study design over time.

The experimental RV challenge model has been critical for our research for several reasons. Most studies of viral infections in asthma are cross-sectional, or prospective studies in design and have been devoted to the evaluation of subjects when they are experiencing acute symptoms. These study designs obviate any chances to evaluate asthma control before the attack occurs; and early, innate, events which occur from the time of virus exposure (or inoculation) to peak symptoms which can have important mechanistic and prevention implications. Using the experimental RV challenge model, we have the opportunity to evaluate the status of our subjects and identify pre-existing risk factors (e.g., airway inflammation) during the run-in period before RV inoculation. Additionally, the subjects in our challenge studies are monitored frequently (at least daily) over the first four days of the infection, which provides important time-sequence information to improve our understanding for the pathogenesis of the asthmatic response to RV.

Because we evaluate mild asthmatic subjects during the RV challenges, this model has some limitations with respect to interpreting and generalizing the results. For this reason, we will continue to compare and contrast the results from RV challenges with our evaluations of actively wheezing children and young adults who require hospitalization or treatment in the emergency room. Taken together, our studies have shown that asthma exacerbations caused by RV are 1) most common in the pediatric population (4); 2) that information in the airway is already present before RV inoculation and is likely to play a critical role in the pathogenesis of an RV-induced asthma exacerbation (8); 3) that it is doubtful that RV by itself causes asthma attacks other than during the infant and toddler years (4,9) indicating that treatments focused on RV may not be sufficient to control asthma; and 4) that asthmatics with a strong allergic phenotype (i.e., with total serum IgE levels >200 IU/ml) are most likely to have inflamed airways when they are infected with RV (8). They are, therefore, more likely to require hospitalization or treatment in the emergency room, as observed in our studies of hospitalized children, studies in the emergency room, and RV challenges (4.8.9).

Additional Safety Background Information: There is now considerable information in the literature describing RV challenges which have been done in North America and in Europe demonstrating that challenges can be done safely in adults (>18 years of age) who have mild asthma. Overall, approximately 100-120 subjects with mild asthma have been challenged with RV at medical centers in the United States and abroad. Collectively, few (no more than 5-10 subjects that we can find in the literature) have required inhaled or oral steroids for asthma symptoms following RV inoculation. There are also no reported cases of hospitalizations or ER visits. Of importance, is that young adults with mild asthma also are at low risk for asthma symptoms requiring hospitalization or emergency room visits when they experience natural infections with rhinovirus. One of the exclusion criteria in our studies is that we will not enroll asthmatics who have required treatment in the hospital or emergency room for asthma during a period of three years prior to enrollment. This is important, because it is very likely that they will have experienced at least one rhinovirus infection (i.e. common cold) during the past three years and this information tells us that our subjects are likely to handle natural RV infections without serious symptoms.

Level of risk associated with the RV-16 challenge for asthmatics with higher levels of total IgE: Since our initial publication of mild asthmatics challenged with RV-16 and others who were challenged with RV-39, we have evaluated 30 asthmatics using essentially the same protocol described in this addendum. After our initial study and prior to the main study, the only criterion for enrollment based on IgE levels was that subjects had to have an IgE level $\geq$ 200 IU/ml. In our published study, 6 subjects had IgE levels between 371 and 820 IU/ml (8). They also had higher levels of expired nitric oxide, blood eosinophil counts, nasal ECP, greater methacholine sensitivity, and chest symptom scores, but none required medical intervention with inhaled or oral steroids. In keeping with our overall hypothesis that allergic inflammation is more likely to persist, is easier to document, and is likely to predict an asthmatic response to RV, the subjects with higher IgE levels in this investigation are more likely to demonstrate significant changes during the experimental challenge as compared to controls, or asthmatics with lower IgE levels.

We have had only one asthmatic subject (total IgE level 1168 IU/ml) whom we treated with oral steroids for wheezing by auscultation on day 5 during the infection. She had no signs or symptoms of respiratory distress and did not experience any increased work of breathing. She improved rapidly (within 2 days) to a 5 day course of steroids. No further treatment was required. Overall, we view the risk of a significant asthma exacerbation in this study to be small based on the fact that none of our subjects (as noted in the exclusion criteria) have required treatment in the ER or hospitalization for their asthma within 3 years prior to their enrollment. Over this period of time we suspect that it is unlikely that any of our participants won't have experienced a natural RV infection and, thus, they have demonstrated that they can tolerate an RV cold without

serious symptoms. Although patients with mild asthma and higher IgE may have more chest symptoms upon experimental HRV infection than patients with lower IgE levels (8), none of the 4 asthmatics who completed the same study protocol last fall required inhaled or oral steroids. Their total IgE levels were: 1429, 1045, 726, and 623 IU/ml. In other words, RV infections in this age group are more likely to cause loss of control, rather than an asthma exacerbation requiring urgent care.

As yet, no challenges have been done in children. Recently, eleven subjects with moderately severe asthma have been challenged with RV-16 in Europe (10). None required oral steroids or hospital care. This does not surprise us, because more serious attacks of asthma caused by rhinovirus in our studies are weighted toward the pediatric population and because these asthmatics were all controlled with inhaled steroids before their RV inoculation. However, we would not be interested to enroll moderately severe asthmatics who are using controller medications in our studies, because these medications obviate our changes of monitoring airway inflammation and changes in lung function during the course of an experimental infection. In other words, these medications would mask changes in airway inflammation and lung function which we need to evaluate as outcome measures in this research. For these reasons, our research will continue to focus on the evaluation of young adults with mild asthma.

Hypothesis to be Tested

Using rhinovirus strain 16 (RV-16) for inoculation, this study design will continue to be used to establish preliminary data and examine mechanisms of the asthmatic response to RV in the atopic host. We have used this same study design over the last decade to evaluate over 40 asthmatic subjects and have made modifications as opportunities have arosen to use new and more sensitive methods of evaluation. We are now planning the enrollment of an additional 24 subjects (12 with mild asthma and 12 non-asthmatic controls) to work out the details of evaluating lymphocyte responses (focused on $CD4^+$ and $CD8^+$ effector T-cells and $CD25^+$ T-regulatory cells) to challenges with RV-16. The main premise for our research is that RV causes exacerbations of asthma by amplifying allergic inflammation present in the airways prior to the onset of the infection. In keeping with this, the primary objective of this investigation will be to test the hypothesis that mild asthmatics enrolled in this study will experience significantly increased lower respiratory tract symptoms over the first 4 days after experimental inoculation with RV-16 than non-allergic, non-asthmatic controls (as shown in our previous studies), and further demonstrate in mechanistic studies that this increase is due to amplified allergic pathways that will serve to guide the development of new treatments to prevent asthma attacks provoked by RV.

Study Design: Biomedical

1. Will controls be used? Yes

2. **What is the study design?** Prospective, time-sequence, case-controlled study

3. **Does the study involve a placebo?** No

Human Participants

Ages 18-40
Sex Both
Race Any
Subjects- see below

1. **Provide target # of subjects (at all sites) needed to complete protocol**. Total of 74 subjects will be evaluated based on current research plans. Thus far, 38 have completed the protocol (i.e., 21 subjects with asthma and 17 non-asthmatic controls. We are planning to enroll an additional 36 subjects (18 with mild asthma and 18 non-asthmatic controls).

2. **Describe expected rate of screen failure/ dropouts/withdrawals from all sites.** Screening for this study is described and covered under IRB# 12656. Among the 38 subjects enrolled under this protocol (i.e., IRB# 12673) there have been no withdrawals or drop outs after starting the run-in period. However, up to10 to 20 % of the subjects who are infected with RV-16 may not develop cold symptoms or have detectable virus in their nasal washes (similar to a sham inoculation). These subjects are dropped from the data analysis and we have incorporated this into our power calculations (see page 8).

3. How many subjects will be enrolled at all sites? 74 including subjects evaluated in the past in addition to those proposed for our current research.
4. How many subjects will sign a consent form under this UVa protocol? 74

Inclusion/Exclusion Criteria

1. List the criteria for inclusion

Subjects with asthma

Criteria for inclusion will include those:

- with physician-diagnosed, mild asthma who are only using bronchodilators (e.g. albuterol) for symptom control.
- Asthma Control Test (ACT) Questionnaire Score a > 19 at enrollment before the inoculation with RV-16 (See Appendix: Asthma Control Test).
- Short-acting beta-agonist use < daily in last 4 weeks
- FEV1 > 70%, or FEV1/FVC ratio > 75% for subjects with FVC values between 80 and 87% predicted whose FEV1 values fall below 70%.a positive methacholine challenge test (i.e. at least a 20% fall in FEV_1) at a methacholine concentration of 16 mg/ml or less (15). The methacholine test will not be done if subjects have used albuterol within 4 hours of the test procedure.Evidence for atopy demonstrated during screening (under IRB protocol# 12656) as judged by positive prick skin tests to one or more aero-allergens.
-

Control subjects. Criteria for inclusion will include those who do not have a history of asthma or allergic disorders (e.g. allergic rhinitis, atopic dermatitis, or food allergies). (This does not include those with hypersensitivity to drugs or insect venoms who are not known to have a higher prevalence of asthma or other allergic disorders..)

2. List the criteria for exclusion

Subjects with asthma

Criteria for exclusion will include those:

- Who test positive for serum neutralizing antibodies at a serum dilution of $\geq$ 1:4 to the strain of virus (currently RV-16) which will be used for the experimental infection.
- Who have required inhaled steroids (used for asthma), nasal steroids (used for allergic rhinitis), cromolyn, nedocromil sodium, ipratropium bromide, or leukotriene modifiers during the month prior to enrollment, oral steroids within 6 weeks of enrollment, omalizumab (Xolair®) within 6 months prior to enrollment, or who are currently using beta adrenergic blocking agents.
- Who have had any upper respiratory tract infections within six weeks prior to enrollment
- Who have been hospitalized or treated in the emergency room (unless the treatment involved the use of a bronchodilator only) for asthma within the last three years.
- Who have required nasal or sinus surgery, excluding surgery for a deviated septum within 12 months prior to enrollment.
- To avoid RV-16 inoculations in subjects with more restrictive lung volumes, those whose FVC is < 80% predicted will be excluded.
- Subjects who have had one or more night time awakenings caused by asthma symptoms and/or who have needed their SABA (albuterol) inhaler for asthma symptoms $\geq$ 4 days during the week before enrollment, or during the week before the inoculation with RV-16.
- Who are pregnant wish to become pregnant during the study, or who are nursing a baby.
- Who have a 5 pack/year history of smoking, or any smoking within the last 6 months.
- Who have a history of chronic illnesses, lung disease other than asthma, congenital heart disease, or immunosuppression.
- Subjects who are currently receiving allergen immunotherapy (IT), or who have received allergen IT within the last 2 years.
- Absolute neutrophil count (ANC) < 1500 cells/mm3 (or 1.5 K/uL) detected during screening within 6 weeks of enrollment, or when rechecked within 2 days of virus inoculation.

Control subjects

Criteria for exclusion will include those:

- Who test positive for serum neutralizing antibodies at a serum dilution of $\geq$ 1:4 to the strain of virus (currently RV-16) which will be used for the experimental infection.
- Who have had any upper respiratory tract infections within six weeks prior to enrollment.
- Who have required nasal or sinus surgery, excluding surgery for a deviated septum within 12 months prior to enrollment.
- Who are pregnant, wish to become pregnant during the study, or who are nursing a baby.
- Who have a 5 pack/year history of smoking, or any smoking within the last 6 months. Who have a history of chronic illnesses, lung diseases, congenital heart disease, or immunosuppression.
- Who have a positive methacholine test, or positive prick skin tests at screening under IRB protocol # 12656.

- Absolute neutrophil count (ANC) < 1500 cells/mm3 (or 1.5 K/uL) detected during screening within 6 weeks of enrollment, or when rechecked within 2 days of virus inoculation.

3. List any restrictions on use of other drugs or treatments. **Restrictions (**if any) **on use of other drugs or treatments:** None, other than restrictions on the medications described above under Criteria for Exclusion for the asthmatic subjects.

Statistical Considerations

1. Is stratification/randomization involved? No

2. **What are the statistical considerations for the protocol?** The primary outcome variable used to compare the response to rhinovirus among the subjects with asthma versus controls will be the cumulative lower respiratory symptoms score monitored during the first 4 days of the infection when symptoms in the lower airway are most likely to occur.

3. **Do you have an adequate sample size, or is your sample size larger than necessary?**

We plan to evaluate an additional 36 subjects 18 with mild asthma and 18 healthy, non-allergic controls). After a 1 week run-in period and following rhinovirus inoculation, each subject will be monitored over 21 days to evaluate their response to infection. In our previous RV challenge studies, no subjects have dropped out. The primary outcome variable for comparing the response to rhinovirus in the subjects with asthma and controls which we have used in our previous study was the mean cumulative lower respiratory tract symptom score measured daily during peak cold symptoms over the first 4 days following virus inoculation (i.e. mild wheeze, shortness of breath, chest tightness, and cough). The same primary outcome variable will be used in this study. Thus, using conservative power calculations, our sample size estimates indicate that we can successfully test our hypothesis if we enroll 36 subjects (18 asthmatics and 18 controls). If 14 subjects complete the study in each group, accounting for approximately a 20% drop-out or failure to develop a cold, we expect to have at least an 80% chance of rejecting the null hypothesis that the cumulative lower respiratory tract symptom score during the first 4 days of the infection will be the same in the asthmatic and control subjects. These power calculations, as well as the plans for primary and secondary variable analyses noted below, were developed by James Patrie, Senior Statistician, Department of Public Health Sciences at UVA. The enrollment of an additional 36 subjects is based on funds available in the Asthma and Allergic Diseases Center at UVA and on recent funding from the NIH. The rationale for increasing our enrollment goals at this point is that it will give us the opportunity to expand our comparison of T-effector and T-regulatory cell responses to RV in asthmatics compared to controls in a larger number of subsets now that new and more sensitive assays have become available. The following is the recent power analysis provided by James Patrie, Senior Biostatistician, Department of Public Health Sciences for the additional 36 subjects.

Power analysis: We plan to enroll 18 subjects with asthma and 18 non-asthmatic subjects. Accounting for a 20% drop out, we expect 14 subjects in each group to complete the study which is 14 more subjects (see below) than needed to achieve the power analysis and enrollment goals calculated by James Patrie, the Senior Statistician collaborating in this project. Note that this is an exploratory study and that new methods for evaluating the immune response to rhinovirus have recently been developed that use the same same blood and nasal wash samples that have been stored. Thus, the enrollment of additional subjects into each arm of this study will allow for more detailed and current data analysis.

Original Power Analyses: If 7 asthmatics and 7 normal healthy controls have day 4 cumulative lower respiratory symptom scores, and if the underlying mean score for the asthmatic population is ≥ 4.2 and the underlying mean score for the health control population is ≤ 0.40, we should have greater than 0.85 statistical power to detect a 3.8 unit difference in the mean cumulative day 4 lower respiratory symptom score, with a two-sided false positive error rate of ≤0.05.

Details: The power of the statistical test was determined based on 1000 Monte Carlo simulation repetitions, in which at each repetition we generated 7 observations from two negative-binomial distributions. The first negative binomial distribution had underlying mean 4.2 and the second negative binomial distribution had underlying mean 0.40. At each repetition of the simulation, we generated a pseudo null permutation distribution for the two sample Wilcoxon test base based on 1000 random shuffles of the negative-binomial distribution group identifies and we then calculated the probability of finding a more extreme p-value than the one calculated based on the original 2 samples (i.e. 7 random variables from a NB(4.2) distribution and 7 random variables from a NB(0.40) distribution). Based on the 1000 simulation repetitions, we then calculated the number of simulation repetitions in which the p-value for the 2-sided permutation test was less than or equal to 0.05 and we divided this number by the total number of simulations (i.e. 1000) to determine the statistical power of the permutation test. The power of the test was 0.88.

4. What is your plan for primary variable analysis?

Primary outcome: Lower respiratory symptom scores from four days of post-inoculation monitoring will be tallied to produce a day 4 cumulative lower respiratory symptom score. These scores will be analyzed by way of a negative binomial generalized linear model. Based on the estimates from the generalized linear model, a set of linear contrasts will be constructed to determine if the mean cumulative symptom score is the same in the 2 study populations. The null hypothesis will be rejected if the p value of the linear contrast is less than or equal to 0.05. A 95% confidence interval will be constructed for each linear contrast. Residual diagnostics will be used to evaluate the goodness of the fit of the model, and a data transformation will be carried out if deemed necessary.

5. What is your plan for secondary variable analysis?

Secondary outcomes: Secondary outcomes will include a comparison of lower respiratory tract symptoms excluding cough (i.e., mild wheeze, shortness of breath, and chest tightness); comparisons of viral replication and clearance; measurements of eNO; selected cytokines, chemokines, and mediators in nasal wash and nasal lining fluid; eosinophil and neutrophil counts in nasal washes, and circulating (blood) eosniophils and regulatory/effector T-cells; and finally gene expression analyses in Rhinoprobe scrapings of the nasal epithelium from asthmatic and control subjects. Data for secondary outcome variables will be collected at baseline, and then again on post-challenge days 1, 2, 3, and 4, and on follow-up days 7, 10, 14, and 21 scheduled in the clinical research center located on the 3rd floor of the new University of Virginia Children's Hosptal (Battle Building). Many of these secondary outcomes will be analyzed by way of repeated measures ANOVA in exactly the same manner as in our previous experimental rhinovirus challenge study (8), a study in which the same rhinovirus-challenge design and strain of rhinovirus (RV-16) was used.

Biomedical Research

1. What will be done in this protocol?
The subjects in this investigation will be enrolled into two groups (18 subjects per group overall) including:

Group 1: Mild asthmatics who are atopic and have a positive methacholine challenge test.

Group 2: Controls who do not have a history of asthma, are not allergic, and have a negative methacholine challenge test

Subjects will be initially screened via IBR-HSR protocol #12656 to qualify for enrollment in this study. Those who qualify and sign the consent form for the study can participate and will start the Run-In period of home monitoring 7 days before virus inoculation (day -7). The samples collected and tests done at enrollment (day -7) and just prior to inoculation with RV-16 will be used to establish baseline values (see below). **Note: Day -7 identifies the day of enrollment which can also be scheduled in the morning one day before (i.e., day -8) or in the morning afterward (day -6) to fit the schedule of those who participate. If possible, however, scheduling the initial enrollment visit on day -7 is optimal and strongly encouraged.**

1. Initial Enrollment Visit (in the morning between 7 AM and noon on Day -7)
    - Urine pregnancy test
    - An administered past medical history questionnaire
    - Physical Exam focusing on eyes, ears, nose, heart and lungs
    - Nasal Wash
    - After the nasal wash an additional nasal specimen will be obtained by using a ASI Rhino-Pro® nasal mucosal curette plastic device to do a light scrapping along the inferior turbinate of each nostril to collect epithelial cells. This will be done using a headlight and a disposable nasal speculum to spread the nares (Bionix) to enhance visibility of the turbinates.
    - Spirometry
    - Expired Nitric Oxide
    - Impulse oscillometry. Impulse oscillometry is a means of assessing respiratory system impedance in a spontaneously breathing patient. In practice, the subject breathes through a mouth seal in line with a loudspeaker that generates a pulse wave lasting 0.1 second that is transmitted down the airways. By generating sound waves of varying frequencies throughout the respiratory cycle, the instrument can evaluate airway patency and resistance at many different levels within the respiratory tree during normal breathing. While spirometry is relatively insensitive with regards to the small airways, oscillometry may provide us with the precision required to evaluate these airways that are more likely to be involved in asthma, particularly during a RV infection. Repeated measurements do not alter pulmonary function, it is suitable for bedside measurements, and it is not effort dependent.

      Method: The technician will place a padded nose clip on the subject's nose to make sure he or she breathes only through his or her mouth. The subject will be asked to hold his or her cheeks so they don't move in or out. The technician will ask the subject to place a sterile mouthpiece into his or her mouth. The subject will be asked to breathe normally. Gentle pulses of air will come through the tube. The technician will then ask the subject to repeat the breathing a few more times to get accurate results..

- Methacholine Challenge
- Blood draw for CBC and differential cell count and serum IgE and immune/T cell analyses (73 ml).
- Provide a dairy card, Microlife hand held monitor, albuterol inhaler and instructions for home monitoring. [Note: Subjects enrolled in this study will now be using and recording their home monitoring data on-line in a template that has been established and maintained in the division of Biomedical Informatics at UVA.

2. Monitoring at home for one week prior to the RV challenge (Run-In Period):

- Each day, subjects will record their upper and lower respiratory tract symptom scores (using the Jackson criteria: Reference #10) on diary cards in the morning (between 6 AM and noon) and in the evening (between 6 PM and mid-night). Lung function tests using the Microlife hand held monitor (www.microlifeusa.com) will also be done daily in the morning (between 6 AM to noon) and in the evening (between 6 PM and mid-night).
- The lung function results will also be written on the diary cards. The Microlife monitor is ATS approved for evaluating peak expiratory flows (PEF) and FEV1 assessments at home.
- An albuterol metered dose inhaler (MDI) will be given to each asthmatic. This inhaler will have a puff counter so that we can monitor the puffs of albuterol which each asthmatic uses daily during the study.

3. **<u>Note:</u> Day 0 in the study identifies the day of inoculation with RV-16. Each subject will have baseline assessments done before (i.e., within 2 days) the hotel stay and virus inoculation. They will then check into the hotel in the evening before virus inoculation. Daily monitoring is scheduled in the morning on Days 0, 1, 2, 3, and 4 as described below to evaluate the effects of the infection.**

Study visit in the morning within 2 days before the hotel stay (done at Elson Student Health or the Clinical Research Unit (CRU) at UVA, or at the Clinical Research Center (CRC) located on the 3rd floor of the new Children's Hospital Outpatient building (Battle Building). All locations are within 10 minutes walking distance from our laboratory and the Asthma and Allergic Diseases Center):

- Spirometry
- Methacholine Challenge
- Oscillometry
- Blood for immune cells, including effector and regulatory T-cell studies, CBC and diff, serum IgE, and baseline RV-16 serology (98 cc)
- Urine for pregnancy test for women who participate and an additional 1 ounces from each subject for measuring an inflammatory metabolite (LTE4) that is expected to increase during the rhinovirus infection.
- Nasal wash
- An additional nasal specimen will be obtained by applying a small piece (1 X 1 cm) of sterile gauze (Surgicel®), routinely used by ENT surgeons at UVA during surgical procedures to provide hemostasis, to inferior turbinate for 4 to 5 minutes in each nostril to collect a sample of epithelial cell lining fluid (about 0.2 ml). [Note: At this point, this will be an exploratory procedure planned for those who participate in the study to provide small amounts of undiluted nasl lining fluid.

- Expired Nitric Oxide and physical exam focusing on eyes, ears, nose, heart and lungs.

4 . Rhinovirus challenge and monitoring during the infection:

In our previous study using rhinovirus-16, significant differences were observed between 6 asthmatic subjects with total serum IgE levels ≥200 IU/ml and 9 healthy controls (i.e., non-asthmatic subjects who have negative tests for allergen specific IgE antibody in their serum , low levels of total serum IgE, and negative methacholine challenge tests)(8).

In our current and future studies, the challenges are planned for the fall months (September, October, or November), or during the spring (March, April, and May). These are months when subjects, mostly university students (undergraduate and graduate) at UVA are attending classes and when allergen exposures in Chalottesville peak. Thus, in keeping with our grant hypothesis, these should be months when asthmatics have a greater susceptibility to the symptom effects of rhinovirus.

All subjects will be admitted in the evening and then stay in the hotel (currently the Holiday Inn Route 29 North in Charlottesville Virginia) over a period of 3 and a half days. After admission to the hotel, the samples collected and testing done in the evening (between 5 and 9 PM) will include:

- Physical Exam focusing on eyes, ears, nose, heart and lungs and a temperature taken P.O.
- Urine pregnancy test will be done in the evening before inoculation.
- Collect and review completed diary card and issue new diary cards
- Complete the Asthma Control Test prior to the inoculation with RV-16. The short Asthma Control Test (see Appendix: Asthma Control Test [ACT]) is focused on asthma control during the month prior to enrollment will be completed. Responding to the 5 questions will take participants 5 minutes. This questionnaire is now validated in studies approved by the NIH.
- Expired nitric oxide
- Spirometry.
- Nasal wash
- Each subject will be given boxes of tissues and ZIP lock freezer bags to put all used tissues into after nose blowing to monitor mucous/secretion weights during the hotel stay (i.e., during the first 4 days after RV inoculation). A detailed protocol for how the tissues and bags will be replaced and the used tissues in bags weighed (2 times daily) is included in the Regulatory Binder for this investigation.
- Inoculation of subjects with RV-16

The inoculation of subjects with rhinovirus (RV-16) will be done by a physician after the nasal wash. For virus inoculation, each patient will be inoculated with 0.25 ml. of RV-16 in each nostril after obtaining the pre-virus inoculation nose wash.. The rhinovirus-16 virus solution used for inoculation will be diluted in HANK's balanced salt solution and will be pre-titered to contain 300-500 $TCID_{50}$/ml. (tissue culture infectious dose 50/ml.). Thus, 75 – 125 $TCID_{50}$/0.25 ml will be instilled into each nostril during the initial inoculation. Five to ten minutes after the initial inoculation, another inoculum (using the same amount of rhinovirus) will be administered.

Following inoculation, subjects will not be allowed to leave their rooms. If they need assistance, they are instructed to call the member of Dr. Heymann's research team, a physician or nurse, who will be staying

in an adjacent room. Each subject will be evaluated and samples will be collected on the day of virus inoculation and daily over the first four days during peak cold symptoms. Physicians and nurses from the University of Virginia Asthma and Allergic Diseases Center, or the Pediatric Respiratory Disease division will be available in the hotel for this study 24 hours a day.

After admission and RV-16 inoculation and daily thereafter until the end of the study, subjects will continue to record on-line their upper and lower respiratory tract symptoms, lung function tests, and puffs of albuterol used on diary cards as described for the Run-In period. If any subject experiences a decline in FEV1 below 70% predicted, or more than 20% from their baseline value at the time of enrollment, they will immediately notify a member of the study team (licensed physician, nurse, or respiratory therapist who will be staying in an adjacent hotel room day and night during the hotel stay). A treatment plan, in accordance with NIH asthma guidelines, will be followed during the course of the infection in the event that changes in lung function occur which are not responding to albuterol (see treatment plan below). Epinephrine, albuterol, and oral steroids will also be readily available to the member of the study team (in their hotel room) to use for treatment. **However, it is <u>uncommon</u> for this to occur among our subjects with mild asthma who are infected with rhinovirus whose FEV1 almost always remain within 20% of their baseline values measured before RV inoculation.**

After admission and RV-16 inoculation (day 0), the following assessments will be repeated in the morning between 7:00 and 9:30 AM (i.e., on days 1, 2, 3, and day 4 in the morning before leaving the hotel, except for spirometry which may be done in the Battle Building CRC later in the morning before the methacholine test):

- subjects will be examined (i.e. a physical examination focused on the respiratory tract, including a temperature as noted above) in the morning by physicians, fellows, and research nurses in our division.
- spirometry
- nasal wash
- ongoing monitoring of mucous weights in the hotel
- expired nitric oxide
- blood sample collection for CBC, and total serum IgE (8 ml)
- after the nasal wash an additional nasal specimen will be obtained by using an ASI Rhino-Pro nasal mucosal curette plastic device to do a light scrapping along the inferior turbinate of each nostril to collect epithelial cells as described above **on day 2 only**.
  an additional nasal specimen will be obtained by applying a small piece of gauze (for 2 minutes) to inferior turbinate in each nostril to collect a sample of epithelial cell lining fluid (about 0.2 ml) **the morning of day 4 only**.
- blood sample collection for immune cell/T-Cells analyses, blood counts, and serum IgE analyses on <u>Day 4 only</u> (120).
- a urine sample (about 1 ounce) will be obtained in the morning for measuring an inflammatory metabolite that is expected to increase during the rhinovirus infection (LTE4) on **Day 4 only.**
- <u>Day 4 only</u> shortly after leaving the hotel (or within 24 hours), subjects will return to the Elson Student Health Respiratory Research Unit or the CRU at UVA for a methacholine test and impulse oscillometry to detect changes during peak cold symptoms.

Study Visits (Days 7, 14, and 21): Note: Study visits on days 7, 14, and 21 can be scheduled in the morning (between 7 AM and noon) one day before or the day after days 7, 14, and 21 following virus inoculation. However, scheduling these visits on days 7, 14, and 21 is optimal and strongly encouraged.

- Physical Exam focusing on eyes, ears, nose, heart and lungs
- Spirometry
- Exhaled Nitric Oxide
- Impulse oscillometry will be repeated on day 7 and 21 only.
- Nasal Wash
- An additional nasal specimen will be obtained by applying a small piece of gauze (for 2 minutes) to inferior turbinate in each nostril to collect a sample of epithelial cell lining fluid (about 0.2 ml) before the nasal wash **the morning of day 14 only**.
- After the nasal wash an additional nasal specimen will be obtained by using an ASI Rhino-Pro plastic device to do a light scrapping along the inferior turbinate of each nostril to collect epithelial cells as described above **on days 7 and 21 only**.
- Methacholine challenge test and urine from female participants for HCG testing at Day 21 only..
- Blood sample collection for CBC, IgE (8 ml) on days 7, 14, and 21. This sample will also be used for RV-16 serology to check for sero-conversion on day 21.
- Additional blood will be obtained for T-cell analyses during the same blood draw, but only on Day 7 (70 ml) and on Day 21 (120 ml).
- Review diaries at every visit and issue new diaries at Days 7 and 14

Study Visit Day 28 - Subjects will complete the Asthma Control Test to summarize their symptoms since the day of virus inoculation (Day 0) and pick up their check for study payment. Note: This study visit can be completed one day before or one day afterward, although completing the Asthma Control Test on day 28 following virus inoculation is strongly encouraged.

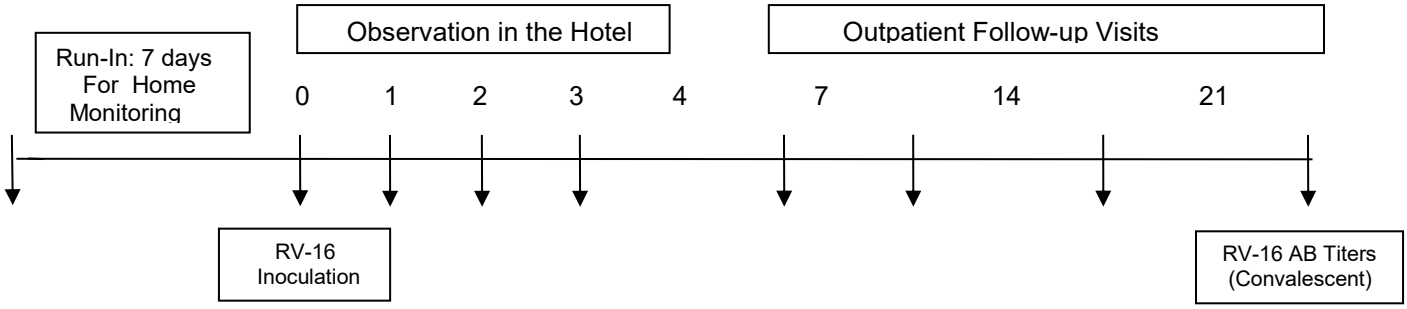
<u>Treatment guidelines should symptom exacerbations occur during the study</u>:
If a study participant experiences an increase in lower respiratory tract symptoms, or a decline in lung function, the following plan describes how subjects will be treated.

- For FEV1 value dropping between 20-29% from the baseline value not responding to albuterol, start on inhaled corticosteroids (Flovent 110 mcg./puff, 2 puffs bid) and discontinue when symptoms return to baseline.
- For FEV1 value dropping between 30- 49% from the baseline value not responding to albuterol, check oximetry and start on inhaled corticosteroid as above and 3 to 5 days of oral steroids (Prednisone 50 mg/day).
- For FEV1value dropping 50% or more from the baseline value. Transportation to the emergency room will be recommended and arranged. Individual stopping rules will apply as described in the Complete Clinical Protocol (Section 8.1.2). Further follow-up and management with the subject's primary care doctor; Dr. Heymann and his study team will continue to be involved and available for follow-up and evaluation 30 days afterward for any subject who requires oral steroids, a visit to the ER, or hospital admission.

Further follow-up and management with the subject's primary care doctor, Dr. Heymann, and his study team will continue to be available for follow-up and management 30 days afterward for any subject who requires oral steroids, a visit to the ER, or hospital admission.

These treatment plans are in keeping with recommendations from the *Guidelines for the Diagnosis and Management of Asthma* (16)

DIAGRAM: EXPERIMENTAL RHINOVIRUS STUDY DESIGN



<u>Note:</u> The diagram does not show a visit to obtain baseline assessments which will be scheduled at the Elson Student Health Center, the Battle Building CRC, or the CRU at UVA within 2 days before virus inoculation as described above. Because we want to be sure that this study does not interfere with classes that university students have, or with weekends, we have created study windows that add flexibility for subjects to participate and that are compatible with the study design. Thus, the Run-In can start a day before, the day of, or the day after the scheduled day of enrollment. The baseline samples can be obtained within 2 days prior to virus inoculation (Day 0), and study visits planned for days 7, 14, and 21 can be scheduled with 24 hours before or 48 hours after the study day (e.g., the day 21 visit can occur on day 20, 21,22, or 23 after virus inoculation). All study visits, however, will be scheduled in the morning (between 7 AM and NOON) to avoid problems with diurnal variations.

2. Will any of the NON-RADIOLOGIC treatments/ procedures be done for research purposes only?
Yes **: <u>All procedures will be done for research purposes only.</u>**

►IF YES, (*examination(s) are performed for research) check one of the following two options:*
__X___The examinations/procedures listed below utilize the same techniques, equipment, etc., that would be used if the subject were to have the examination(s) performed for clinical care. There exists the potential for the discovery of clinically significant incidental findings.

- The PI takes full responsibility for the identification of incidental findings:

- The PI will inform the subjects must be informed verbally of all incidental findings that are of clinical significance or are of questionable significance**.**
- A follow-up letter describing the finding should be provided to the subject with instructions to either show the letter to their PC or if the subject has no PCP, the subject should be instructed to make an appointment at UVa or at the Free Clinic**.**

Examinations/procedures:

- Blood sample for eosinophil counts and IgE responses.
- Urine Pregnancy Test
- Allergy testing
- Lung function testing using a Microlife monitor at home daily
- Spirometry
- Methacholine Challenge Test
- Exhaled Nitrous Oxide
- Asthma Control Test

__**X**__This examinations/procedures listed below utilize non-standard/investigational, equipment, etc. It is impossible to determine the significance of such results, therefore abnormalities will not be shared with the subject because the meaning of the exam is not yet proven and is of unknown clinical benefit.

Examimations/procedures:

- Rhinovirus Inoculation
- Urine collection for inflammatory markers
- Nasal Wash
- Monitoring mucous weights and secretions during the hotel stay
- Oscillometry
- Rhinoprobe® and nasal gauze sampling
- Immune testing focused on blood dendritic cells and lymphocytes (T regulatory and effector T cells).

3. Will any RADIOLOGIC treatments/examinations be performed for research purposes only? N/A

4. If a potential subject does not meet the inclusion/exclusion criteria will you repeat any of the screening procedures/tests? Yes. For example, subjects who have had an upper respiratory tract infection within 6 weeks of enrollment, may be rescreened at a later date for subsequent participation.

5. If the study involves drawing blood, will the blood be drawn from a central or arterial line? No

6. Will you be using viable embryos? No

7. Will you be using embryonic stem cells? No

Specimens: Not to be Used for Genetic Research or Banking

Specimen Information

1. Describe the type of specimen to be used: Blood, nasal washes, and urine for LTE4 assessments from all subjects. Urine from women of childbearing potential for HCG testing will also be obtained during the screening and before the virus challenge. ASI Rhino-Pro scrapings for epithelial cells from all subjects. Gauze applications to nasal inferior turbinates to collect nasal lining fluid from all subjects.

2. Will the specimen be obtained BEFORE a subject has signed a consent form? No

3. Will you be using discarded specimens? No

Specimen Labeling

1. What information/ HIPAA identifiers will be on the specimen label when it is given to the study team (from clinical labs or other source outside the study team) and/or what information will you put on the specimen?

Subject number, sample date, study code (e.g. RVL indicating that these samples will be used to evaluate RV infections and Lymphocytes), and specimen type (e.g. B for blood)

2. If the specimen is given to the study team with information on the label will you delete any of the information on the specimen label? No

3. Will any additional data be linked to the specimen by way of a code? Yes, specimens will be coded and linked to the data collected to the data collected for this study. Only the study team members will have access to the study data.

4. Will the analysis on the specimen be done soon (within 24 hours) after it is collected? Only for HCG testing.
►**IF NO, where will the specimen be stored until analysis is done?** Other specimen's will be stored frozen at – 80 C. in freezer in Dr. Heymann's (the study PI) laboratory in MR-4 (Room # 5060) IBC#128-01

Specimen Shipping
1. Do you plan to ship any specimens outside of UVA? Yes. Rhinoprobe® samples
►**IF YES, answer the following questions:**

2. To whom will the specimen be shipped? Analysis will be done either at Northwestern University or the University of Cincinnati (arrangements to be finalized).

3. What will the outside site do with the specimens? Analysis of Rhinoprobe® samples

4. What information that will be on the specimen label when the specimen is sent outside of UVa.? Study ID number and date of collection

5. Will any additional information be sent with the sample? No

6. Will any HIPAA identifiers will be sent out with the specimens? No

Specimen Banking at UVa

Information Accompanying Specimens or Data

1. What information will be on the label of the specimen? Subjects study enrollment number (e.g., 001 = subject number 1), type of sample (i.e. NW = nasal wash, B = blood), and date sample collected.

2. What information will be "linked to" or will accompany the specimen? Subject number will be on the specimen collected. This subject number will also be on the enrollment log that will be linked to the subject's name. Information that will be "linked" to each sample will include each subject's responses to their questionnaires completed during screening (under IRB# 12656) to validate and provide more information about their asthma. This information will be stored on a computer (password protected) in the P.I.'s laboratory) and will only be accessible to the P.I. and his staff who will be directly involved with the enrollment and monitoring of subjects while they are in this study.

3. If the samples are identifiable (have HIPAA identifiers**) explain why they cannot be coded or de-identified.** N/A

Collection and/or Storage of Specimens

4. How much material (e.g. blood, tissue) will be collected and how will it be collected?
Blood: 517 ml of blood will be collected via venipuncture over the duration of the study (4 weeks).
Nine nasal washes (5ml/wash) will be obtained during the study.
Three Rhinoprobe® and gauze samples of nasal lining fluid will be obtained during the study as noted above.

5. Could the loss of confidentiality of the subject's health information potentially have a negative impact decisions of health coverage, employment, insurability or any other benefit, or cause social stigmatization? No. The nasal scrapings are being done to investigate how genes expressed by the lining cells in the nose (called epithelial cells) respond to changes in the environment, specifically in this study in response to exposure to the common cold virus (rhinovirus) or environmental allergen exposure. The changes in gene expression will be monitored by RNA sequencing and epigenetic testing. Importantly, the results from these scrapings will not be used to identify a participants genetic background or risk factors for disease and genomic DNA analyses will not be done.

6. Who will be responsible for storing the specimens? Peter Heymann MD

7. Will the specimen be stored at UVa? Yes

►**IF YES, where will the specimens be stored?** Peter Heymann's Laboratory in MR-4

8. Will another research institution or entity outside of UVa ever have control over the specimens? Yes. Nasal scraping samples for analyzing epithelial cell gene expression via RNA seq will be sent to a research collaborator at the University of Cincinnati under an MTA. These samples will be 'key and coded'. The only information recorded on the samples is described above (see "Information Accompanying Specimens"). No access to HIPAA identifiers will be available to our collaborators.

►IF YES, answer the following questions.

8a. What is the name of the outside institution/entity?
Answer/Response: The University of Cincinnati

8b. What information will be on the specimen label when the specimen is sent outside of UVa?

Answer/Response: Subjects study enrollment number (e.g., 001 = subject number 1), type of sample (i.e. NW = nasal wash, B = blood), and date sample collected.

8c. Will any additional information be sent with the sample? No

EXAMPLE: clinical information, HIPAA identifiers located on a separate piece of paper/ computer file

Answer/Response:

►IF YES, list what will be sent.
Answer/Response: N/A

INSTRUCTIONS:
Note to Study Team: If you plan to ship specimens outside of UVa, personnel performing this function must have taken the appropriate training from the Department of Transportation. Contact SOM CTO for training information.

Note to IRB Staff: If the information sent outside of UVa with the specimen meets the criteria of "Identifiable" and the study does not have a consent form- the disclosure would require Tracking under HIPAA regulations. If it meets the criteria of a Limited Data Set, a Data Use Agreement will be required.

9. Can participants withdraw their specimens or request that they be destroyed? Yes

Genetic Research

Background

1. Briefly describe the nature and purpose of the genetic research (what will be tested and how):
Answer/Response: The nasal scrapings are being done to investigate how genes expressed by the lining cells in the nose (called epithelial cells) respond to changes in the environment, specifically in this study in response to exposure to the common cold virus (rhinovirus) or natural environmental allergen exposure.

2. Could any genetic findings affect current treatment or therapy?
Answer/Response: The results will hopefully provide new information that will have therapeutic implications.

Risks of Genetic Research

INSTRUCTIONS: Most genetic risk is probably future risk. It may be difficult now to anticipate confidentiality risks that participants may face one, five or ten years from now by being in this study at this time because the technology is not yet developed. In the future, it is possible that genetic testing results will be used more broadly by employers or insurers or considered by them. Since it is difficult to assess that risk now, participants should be provided with information that informs them of that uncertainty and the possibility that risk not present now may exist in the future. Sometimes the actual study will be important in determining the

future uses of such testing; in that case, provisions should be made to inform participants of any risks that become more apparent as the study progresses.

Answer/Response: We will be evaluating how genes expressed (turned off, or turned on) by epithelial cells lining the mucosal surface of the nasal turbinates are responding to environmental stimuli (e.g., the rhinovirus infection or natural environmental allergen exposure). The methods used will involve RNA sequencing and epigenetic testing. No genomic DNA analyses will be done using these samples and no data will be generated that will identify a participant's genetic identity or risk factors for disease.

1. Risks of Accidental Disclosure/Loss of Confidentiality

INSTRUCTIONS: Many risks associated with genetic research are related to breaches in confidentiality. You should consider the mechanisms through which breaches might occur and the consequences of those breaches. Risk is related to the amount of data stored about a subject, the security of the data storage, the more likely linkages, and the seriousness of any condition related to the data.
Where the genetic study is linked to an already diagnosed disease, the risk to the subject may be minimal, but there may still be some significant risk to the family.

1.a. If there were an accidental disclosure of this research data, could it affect either the subject or the subject's family member(s)?
Answer/Response: N/A

►IF YES, explain how:
Answer/Response: N/A

1.b. What data will you be keeping about a subject?

Examples: genetic results, clinical data related to the results, etc.
Answer/Response: Clinical data related to the participant's allergies and asthma.

1.c. Where are you keeping this data and/or specimens?

Examples: central registry, central repository, data on excel spreadsheet maintained by study team
Answer/Response: The data (password protected) will be maintained by the study team in Dr. Heymann's laboratory on an excel spreadsheet.

1.d. Are there any documented correlations or associations that might be outside the study?

Examples: a study focusing on correlations between APOE-4 and brain trauma may reveal information about a participant's risk for early-onset Alzheimer's Disease even though that information is not part of the actual study.
Answer/Response: N/A

2. Social risks

INSTRUCTIONS: Misconceptions are often an important source of potential discrimination. Recent studies have shown that employers often fail to distinguish between having a genetic mutation and the possibility of becoming symptomatic with a disease.

Examples of types of social risks: health insurance, life insurance, disability insurance, employment, stigmatization, stress upon family relationships, change in reproduction plans, immigration status, forensic implications, and mistaken paternity. While we have federal and state legislation that protects some of this information, it does not cover many types of insurance, and data show that even with it, some discrimination still occurs. Keep in mind that these risks may vary; a condition that implicates disability insurance may have a minimal impact on life insurance.

Answer/Response: N/A

2.a. If there were a deliberate or accidental disclosure of the results or associated data from this research, could an insurer or employer think that it would affect the insurability or employability of the subject?

INSTRUCTIONS: Do not consider any legal restrictions on use of the information

Example, if a long-term care insurer has received information about a subject's APOE4 status, the status would affect the subject's insurability.

Answer/Response: No

2.b. If there were a deliberate or an accidental disclosure of the results or associated data from this research, could it affect reproductive plans of the subject or the subject's family member(s)?

Answer/Response: No

►IF YES, explain how:

Answer/Response: No

2.c. If there were a deliberate or an accidental disclosure of the results or associated data from this research, could it stigmatize the subject?

Examples: alcoholism, drug abuse, gender identity issues, dementia, etc.

Answer/Response: No

►IF YES, explain how:

Answer/Response:

3. Psychological risks

Example: impact of results, impact of disease knowledge without treatment, disclosure of vague or uncertain results, stress related to other family members

3.a. If there were a deliberate or an accidental disclosure of the results or associated data from this research, could this cause psychological stress to the subject or a family member (include rational and irrational reactions)?

Example, if a child is diagnosed with a genetic condition, might a parent feel responsibility or guilt?

Answer/Response: No

4. Harm to the community

4.a. If your study involves an ethnic or cultural group, will the results affect that community?
Answer/Response: No

►IF YES, explain the risks:

Example: could the genetic information be used to cause a group or community of people to be vulnerable to discrimination based on actual or perceived associations, e.g. Ashkenazy Jews and the BRCA genes, or alcoholism or other addictions within ethnic or cultural groups?

Where a study may raise community risk, it may be a good idea to conduct focus group discussions with community representatives before the protocol is finalized.

Answer/Response:

4.b. How will the risks listed above be minimized?
Answer/Response: N/A

4.c. How will these risks be communicated to participants?

Example: subjects will be notified of the risks during the consenting process

Answer/Response: N/A

Information Accompanying Specimens or Data to be Used for Genetic Research

1. **What information will be on the label of the specimen to be used for genetic research?**

INSTRUCIONS: The IRB STRONGLY advises that you do not include HIPAA identifiers such as name, medical record number, subject initials on the label. If HIPAA identifiers will be included- you must provide a STRONG justification for this procedure.

Answer/Response: The information will be de-identified and only include the subjects study enrollment number (e.g., 001 = subject number 1), type of sample (i.e. NW = nasal wash, B = blood), and date that the sample was collected.

2. **What information will be "linked to" or will accompany the specimen to be used for genetic research?**

Examples: type of clinical information, type of demographic data, HIPAA identifiers such as name, Medical Record Number

Answer/Response: Clinical data (password protected) related to the participant's allergies and asthma will be maintained in Dr. Heymann's laboratory which can be "linked to" the specimen. However, none of this information will accompany the de-identified specimens.

3. **If identifiers will be linked to specimens/ data, when will the identifiers be destroyed?**

_____ NA- No identifiers
_____ After specimen is linked to clinical data but before genetic analysis is completed.
_____ After specimen is linked to clinical data and immediately after the genetic analysis for the individual participant is completed.

_____ After specimen is linked to clinical data and immediately after the genetic analysis for all participants is completed
__X___ Link to identifiers will not be destroyed
_____ Other : Specify Answer/Response:

Confidentiality and Collection/Storage of Specimens to be Used for Genetic Research

1. **Will any information/ the consent form/ results regarding genetic research be placed in the participant's medical record?**
   Answer/Response: No

2. **How much material (e.g. blood, tissue) will be collected for genetic research and how will it be collected?**
   Answer/Response: _After a nasal wash, a small sample of epithelial cells will be obtained by using a ASI Rhino-Pro® nasal mucosal curette plastic device. The ASI Rhino-Pro® will be used to do a light scrapping along the inferior turbinate of each nostril to collect the epithelial cells. This will be done using a headlight and a disposable nasal speculum to spread the nares (Bionix) to enhance visibility of the turbinates. The RNA for sequencing will be extracted from these scrapings.

3. **Who will be responsible for storing the specimens for genetic research?**
   Examples: sponsor, UVa PI, tissue bank/procurement facility, tissue bank outside of UVa?
   Answer/Response: Peter W. Heymann, MD (Study PI)

4. **If stored at UVa-where will the specimens to be used for genetic research be stored?**
   Examples: a refrigerator/freezer in a lab, a room-provide room number, or specific location
   To protect confidentiality, whenever possible, you should consider using a central facility/repository such as the UVa Biorepository and Tissue Research Facility.
   Answer/Response: - 80 degree freezer in Dr. Heymann's laboratory (Building MR-4; Room 5060)

5. **Will another research institution or entity outside of UVa ever have control over the specimens?**
   Answer/Response: Yes

   ►IF YES, list the name of outside institution/entity.
   Answer/Response: The University of Cincinnati Children's Hospital

6. **List the information that will be on the specimen label when the specimen is sent outside of UVa.**
   Answer/Response: As noted above, the information will be de-identified and only include the subjects study enrollment number (e.g., 001 = subject number 1), type of sample (i.e. NW = nasal wash, B = blood), and date that the sample was collected.

7. **Will any additional information be sent with the sample?**

Examples: clinical information, HIPAA identifiers located on a separate piece of paper/ computer file

Answer/Response: No

►**IF YES, list what will be sent.**
Answer/Response:

Note to Study Team: If you plan to ship specimens outside of UVa, personnel performing this function must have taken the appropriate training from the Department of Transportation. Contact SOM CTO for training information.

Note to IRB Staff: If the information sent outside of UVa with the specimen meets the criteria of "Identifiable" and the study does not have a consent form- the disclosure would require Tracking under HIPAA regulations. If it meets the criteria of a Limited Data Set, a Data Use Agreement will be required.

8. **Can participants withdraw their specimens or request that they be destroyed?**

The answer to this question must be YES unless the specimens are stripped of all HIPAA identifiers.

Answer/Response: Yes

Third Party Concerns

1. **Will family members be directly involved in the research?**

Answer/Response: No

►**IF YES, how and by whom (*e.g., an investigator, the participant, a support group)* will those family members be recruited?**
Answer/Response: N/A

►**IF NO, does this study have any implications for the participant's family members?**
Answer/Response: No

►**IF YES, will that information be shared with relevant family members?**
Answer/Response: N/A

Genetic Research Results Not Disclosed to Subjects

1. **Briefly describe the nature and purpose of the genetic research (what will be tested and how).**
Answer/Response: See Genetic research section qn#1.

2. **Why will you not disclose genetic research results to subjects?**
Answer/Response: The research has not clinical significance at this time.

3. **If future research yields results that are clinically meaningful or significant, would those results be disclosed to the participant? Why or why not?**

Answer/Response: Yes, if those results are clinically meaningful in the future.

4. **Even if results may not be clinically valid (*recognized by FDA or generally recognized by practitioners in the field as established*), might they affect a subject's clinical care?**
Answer/Response: No

►IF YES, how?
Answer/Response:

Data and Safety Monitoring Plan

1. Definition:

1.1 How will you define <u>adverse events</u> (AE)) for this study?

__X___An adverse event will be considered any undesirable sign, symptom or medical or psychological condition **even if the event is not considered to be related** to the investigational drug/device/intervention. Medical condition/diseases present before starting the investigational drug/intervention will be considered adverse events only if they worsen after starting study treatment/intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research. Adverse events also include any problems associated with the use of an investigational device that adversely affects the rights, safety or welfare of subjects.

1.2 How will you define <u>serious adverse events</u>?

__X__A serious adverse event will be considered any undesirable sign, symptom, or medical condition which is fatal, is life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/incapacity, constitutes a congenital anomaly or birth defect, is medically significant and which the investigator regards as serious based on appropriate medical judgment. An important medical event is any AE that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions of SAEs.

1.3 What is the definition of an <u>unanticipated problem?</u>

Do not change this answer

An unanticipated problem is any event, experience that meets ALL 3 criteria below:

- Is unexpected in terms of nature, severity or frequency given the research procedures that are described in the protocol-related documents AND in the characteristics of the subject population being studies
- Related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.
- The incident suggests that the research placed the subject or others at greater risk of harm than was previously known or recognized OR results in actual harm to the subject or others

1.4 What is the definition of a protocol violation?

Do not change this answer

A protocol violation is defined as any change, deviation, or departure from the study design or procedures of a research project that is NOT approved by the IRB-HSR prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations. Protocol violations may or may not be under the control of the study team or UVa staff. These protocol violations may be major or minor violations.

Additional Information: see the IRB-HSR website at http://www.virginia.edu/vpr/irb/HSR_docs/Forms/Protocol_Violations_%20Enrollment_Exceptions_Instructions.doc

1.5 **If pregnancy occurs how will this information be managed?** Female subjects know that pregnancy is an exclusion criteria for participation in this study. An HCG screen will also be done before virus inoculation and subjects excluded if the test is positive. During the 3 weeks of monitoring during the cold, we will not know if the subjects become pregnant, but this is unlikely and there is no reason to believe that the experimental rhinovirus infection will have any adverse effects on the fetus different from a natural cold.

_____ Adverse Event- will follow adverse event recording and reporting procedures outlined in section 3.

_____ Unanticipated Problems- will follow Unanticipated Problem recording and reporting procedures outlined in section 3.

__X___ Other- will follow op to obtain outcome information that will be documented in the source documents in the subject's study binder

1.6 What is the definition of a Protocol Enrollment Exception?

___X__NA- No outside sponsor

1.7 What is the definition of a data breach?

Do not change this answer

A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

Additional Information may be found on the IRB-HSR Website: Data Breach

2. Identified risks and plans to minimize risk

2.1 What risks are expected due to the intervention in this protocol?

Expected Risks related to study participation.	**Frequency**
Viral Inoculation	
Cold Symptoms	__X__ Occurs frequently

Mild wheezing Chest tightness	____Occurs infrequently ____Occurs rarely ____Frequency unknown
Worsening asthma symptoms	_X__Occurs frequently, although mild ____Occurs infrequently __Occurs rarely ____Frequency unknown
Other risks: • Rhinovirus infections may infrequently be associated with ear infections or sinus infections. Ear infections cause ear pain (earache) and sinusitis [an inflammation of the sinuses (hollow spaces in the bone of the cheeks and forehead) due to an infection] may cause sinus pressure or pain. These complications have been uncommon in volunteers experimentally infected with rhinovirus. If these infections develop they can be treated with antibiotics. If antibiotics are required the PI will prescribe the antibiotics but you will be responsible for buying the antibiotics. • A transient decline in blood cells (neutrophils) which are used to fight bacterial infections is common, but serious declines below 1000 cells/mm3 or serious sinus infections linked to infections with the common cold virus (rhinovirus) are uncommon and have not yet been observed. • Serious bacterial infections (such as pneumonia). • The virus that will be used for the study is a rhinovirus that was isolated from a volunteer in a previous study. The donor volunteer was tested for HIV (AIDS), hepatitis C, and	X Occurs infrequently (uncommon in experimental colds) X Occurs infrequently. X Rare. This problem has never occurred. X Rare. This problem has never occurred.

hepatitis B infection and found to be negative. After isolation, the virus was tested for the presence of other germs associated with infections in humans. Although none were found there is a remote chance that an unknown pathogen could be present and cause infection. This problem, however, has never occurred. The safety testing done on this virus has been reviewed by the FDA and the FDA has given us permission to use the virus for these experimental studies.	
Risks of Spirometry	
Dizziness Coughing	__Occurs frequently _X___Occurs infrequently ____Occurs rarely ____Frequency unknown
Shortness of breath Mild respiratory fatigue Chest tightness Chest soreness Fainting	__Occurs frequently _X_Occurs infrequently ____Occurs rarely ____Frequency unknown
Methacholine Challenge Testing	
Chest tightness Cough	__X__Occurs frequently ____Occurs infrequently ____Occurs rarely ____Frequency unknown
Dyspnea Wheezing Lightheadedness Increased respiratory secretions Pruritis Headache Throat Irritation	___Occurs frequently __X_Occurs infrequently ____Occurs rarely ____Frequency unknown
Difficulty breathing	___Occurs frequently ____ Occurs infrequently __X_Occurs rarely ____Frequency unknown
Severe asthma attack during testing	__X_Occurs rarely
Risks of Albuterol	
Mild throat irritation Cough	___Occurs frequently __X_Occurs infrequently

Increased pulse rate Mild tremor Headache Dizziness Insomnia Sweating Nausea Vomiting Dry Mouth	____Occurs rarely ____Frequency unknown
Allergic Reaction Chest pain	___Occurs frequently ___ Occurs infrequently __X_Occurs rarely ____Frequency unknown
Risks of Nasal Wash	
Coughing Nasal Irritation Monitoring of nasal mucous weights	___Occurs frequently __X_Occurs infrequently ____Occurs rarely ____Frequency unknown No risk,
Risks of Exhaled Nitrous Oxide Feeling of light headedness if subjects blow to hard	__X_Occurs infrequently
Risks of Sterile Surgicel Guaze (1 X 1 cm) Applications to the Nasal Inferior Turbinates to collect Nasal Lining Fluid Mild to moderate irritation Sneezing	X Mild to moderate irritation occurs frequently and resolves quickly X Sneezing occurs occassionally
Impulse Oscillometry Mild light-headedness and coughing, shortness of breath, and/or chest tightness.	X Occurs infrequently (reversed with inhaled albuterol).
Phlebotomy	
Phlebotomy: local discomfort and bruising	_X_Occurs frequently ____Occurs infrequently ____Occurs rarely ____Frequency unknown
Phlebotomy: vasovagal reactions	____Occurs frequently ____Occurs infrequently _X_Occurs rarely ____Frequency unknown
Risks of ASI Rhino-Pro ® sampling	
Tingling Sneezing Epstaxis (easily stopped using standard treatment – i.e., applying pressure to the outside of the nose)	___Occurs frequently ___X _Occurs infrequently; the procedure takes 30 seconds. ____Occurs rarely ____Frequency unknown

Nose bleed	____Occurs frequently ____Occurs infrequently _X_Occurs rarely ____Frequency unknown
Nasal Bleeding	____Occurs frequently ____Occurs infrequently _X_Occurs rarely ____Frequency unknown

3.2 List by bullet format a summary of safety tests/procedures/observations to be performed.

- Adequate screening including Pregnancy Testing
- Pulse Oximetry (should symptom exacerbations occur as noted in the Treatment Plan above, pg. 13)
- Physical Exams
- Spirometry
- Daily home symptom and FEV_1 monitoring.
- Physicians and/or nurses, or respiratory therapists from the University of Virginia Asthma and Allergic Diseases Center, or the Pediatric Respiratory Disease division will be on site in the hotel 24/day for the duration of the subjects' hotel stay. The study team on site will provide monitoring of the study subjects and will be available as needed to the study subjects. In addition, epinephrine, albuterol, and oral steroids will be readily available to the member of the study team to use for treatment if necessary.

2.3 Under what criteria would an INDIVIDUAL SUBJECT'S study treatment or study participation be stopped or modified

__X___At subject, PI or sponsor's request

__X__Study procedures would stop if the subject had a serious adverse event deemed related to the study. See description of SAE's above..

X If, after inoculation with the RV-16 pool, two subjects experience severe asthma exacerbations requiring oral steroids for $\geq$ 5 days annually (during the spring or fall enrollments), or if 1 subject requires treatment in the ER with systemic steroids, or hospitalization at any time during the study. Among the last 46 asthmatic subjects challenged with RV, only one subject required intervention with a 5 day course of oral steroids, but did not require treatment in the ER or hospitalization (which has never occurred in our rhinovirus challenge studies). Because the exclusion criteria (see below) obviates the enrollment of subjects who have required treatment in the ER, or hospitalization during the last 3 years (or any intubation ever requiring management in an intensive care unit), we suspect that it is not likely that the above stopping rules will be encountered.

X If 2 subjects developed a significant lower tract infection (not including bronchitis) following RV-16 inoculation and this will lead to stopping the study for further review. Lower respiratory tract infections have not yet occurred during experimental (or even natural) infections with rhinovirus in an immune competent host, because this pathogen is not known to be a cause of pneumonia. It is conceivable, however, that one or two subjects could acquire another respiratory tract pathogen that could cause a lower respiratory tract infection.

X An absolute neutrophil count < 1000 cells/mm3 detected in CBC and differential cell counts at any time during the study.

X A blood hemoglobin level < 10.0 g/dL detected in CBC and differential cell count at any time during the study, in keeping with a NCI-CTCAE grade one adverse event.

X Death: One death will lead to stopping the study until an expedited review is completed to determine whether the death might have resulted from any of the study procedures.

2.4 Under what criteria would THE ENTIRE STUDY need to be stopped.

__X__Per IRB, PI, DSMB, or sponsor discretion

__X___Other: This study would also be stopped if more than two subjects required oral steroids for asthma symptoms following RV inoculation, or if more than one emergency room visit or hospitalization occurred. Thus far, no emergency room or hospitalizations have occurred in our studies and none, that we are aware of, have been described in the literature.

2.5 What are the criteria for breaking the blind/mask?

__X__NA – Not blinded/masked

2.6 **How will subject withdrawals/dropouts be reported to the IRB prior to study completion?**

___X__IRB-HSR continuation status form

3. Adverse Event / Unanticipated Problem Recording and Reporting

3.1 Will all adverse events, as defined in section 1.1, be collected/recorded? Yes

3.2 How will adverse event data be collected/recorded?

_X____Paper AE forms/source documents

3.3. How will AEs be classified/graded?

__X__ All adverse events whether or not listed in the NCI-CTCAE will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual (A semi-colon indicates 'or' within the description of the grade.):

Grade 1 = Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 = Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).
Grade 3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL (bathing, dressing and undressing, feeding self, using he toilet, taking medications, and not bedridden).
Grade 4 = Life-threatening consequences; or urgent intervention indicated.
Grade 5 = Death related to AE

3.4 What scale will the PI use when evaluating the relatedness of adverse events to the study participation?

___X__The PI will determine the relationship of adverse events to the study using the following scale:

Related:	AE is clearly related to the intervention
Possibly related:	AE may be related to the intervention
Unrelated:	AE is clearly not related to intervention

3.5 When will recording/reporting of adverse events/unanticipated problems begin?

__X__After subject begins study drug/ device placement/intervention /study-related procedure/specimen collection

3.6 When will the recording/reporting of adverse events/unanticipated problems end?

__X___Subject completes intervention and follow up period of protocol. An adverse event will be followed until any of the following takes place: a) it is resolved, b) participant is stable, c) a minimum of 30 days after participant is terminated from the study and the NIAID Medical Officer and the Principal Investigator determine that follow-up is complete. If an abnormal value or result from a clinical or laboratory evaluation (e.g., a radiograph, an ultrasound, or an electrocardiogram) is determined to be an AE (refer to National Cancer Institute's Common Terminology Criteria for Adverse Events Version , Version 4.0, May 2009) , then the

evaluation that produced the value or result can be repeated until the value or result returns to normal, or the result can be explained, or the usual standard of care does not require further follow-up, and the participant's safety is not at risk.

3.7 How will Adverse Events, Unanticipated Problems, Protocol Violations and Data Breaches be reported? Complete the table below to answer this question

Type of Event	**To whom will it be reported:**	**Time Frame for Reporting**	**How reported?**
Any internal event resulting in death that is deemed possibly related to (caused by) study participation (Note: An internal event is one that occurs in a subject enrolled in a UVa protocol.)	IRB-HSR & NIAID MO: Lisa Wheatley, MD, MPH 240-627-3573 lisa.wheatley@nih.gov	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/
Internal, Serious, Unexpected adverse event	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. Notification to the NIAID MO – within 1 calendar day from the time the study team received knowledge of the event. *Timeline includes submission of signed hardcopy of AE form.*	IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not adverse events or protocol violations This would include a Data Breach.	IRB-HSR & NIAID MO	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. *http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc)*

Protocol Violations (*The IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by your sponsor, if applicable.)* Or Enrollment Exceptions	IRB-HSR & NIAID MO	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation and Enrollment Exception Reporting Form *http://www.virginia.edu/vprgs/irb/hsr_forms.html*
Data Breach	The UVa Corporate Compliance and Privacy Office, a ITC: if breach involves electronic data- UVa Police if breach includes such things as stolen computers. NIAID MO	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 **ITC:** Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html Phone- (434) 924-7166

UVa PI HELD IND/IDE			
Life-threatening and/or fatal unexpected events related or possibly related to the use of the investigational agent.	FDA	Within 7 calendar days of the study team learning of the event	Form FDA 3500A (MedWatch) or narrative
Serious, unexpected and related or possibly related adverse events	FDA	Within 15 calendar days after the study team receives knowledge of the event	Form FDA 3500A (MedWatch) or narrative
For Device Studies: Unanticipated adverse device effects (internal or external)	FDA	Within 10 working days of the study team receiving knowledge of the event	Form FDA 3500A (MedWatch) or narrative
All adverse events	FDA	Annually	IND annual report

4. How will the endpoint data be collected/recorded.

__X__Source documents

5. Data and Safety Oversight Responsibility

5.1. Who is responsible for overseeing safety data for this study ?

___X__ Oversight by DAIT/NIAID Medical Officer and Safety Monitoring Committee (SMC) with monitoring visits from Pharmaceutical Product Development on a contract from DAIT/NIAID (*skip question 5.2*)

5.2. What is the composition of the reviewing body and how is it affiliated with the sponsor?
The SMC is composed of physicians and statisticians convened by DAIT/ NIAID with expertise in clinical allergy and asthma trials. Ad hoc members are recruited as needed for content expertise.

5.3. What items will be included in the aggregate review conducted by the PI?

___X__All adverse events

__X___Unanticipated Problems

_____Protocol violations

_____Audit results

_____Application of dose finding escalation/de-escalation rules *These should be outlined under 2.4.*

_____Application of study designed stopping/decision rules

_____Early withdrawals

_____Whether the study accrual pattern warrants continuation/action

_____Endpoint data

5.4 **How often will aggregate review occur?**
For additional information on aggregate review see:
www.virginia.edu/vpr/irb/hsr/continuations.html#aggreview

___X__Annually

5.5. How often will a report, regarding the outcome of the review by the DSMB/DSMC, be sent to the UVa PI? N/A

5.6. How will a report of the information discussed in question 5.4 OR 5.5 be submitted to the IRB?

___X_Part of IRB-HSR continuation status form

Payment

1. Are subjects being reimbursed for travel expenses (*receipts /mileage required***)?** Yes. Participants from other Universities (i.e., from the Richmond area [VCU and J. Sargent Reynolds], Staunton/Harrisonburg area (JMU and Mary Baldwin), Lexington area (Washington and Lee), or the Lynchburg area (Liberty University), will also be reimbursed $30.00 per trip for their travel expenses to UVA for Visits Number 1 through 8. Our grant funding is insufficient to reimburse on a per mileage basis, but we are not enrolling students who attend Universities that are more than 90 miles away and the $30 payment is clearly stated in the ICF.

2. Are subjects compensated for being in this study? Yes

2a. What is the maximum TOTAL compensation to be given over the duration of the protocol? **$**920

2b. Explain compensation to be given- By check

2c. Is payment pro-rated (*e.g. some compensation is given even if subjects do not complete the entire study)?* Yes

2. Is money paid from UVa or State funds (including grant funds)? Yes

3a. How will the researcher compensate the subjects?

___X_ Check issued to participant via UVA Oracle or State system

3b. Which category/ categories best describes the process of compensation?

___X__ All compensation will be made via check issued to participant via UVA Oracle or State system

Risk/ Benefit Analysis

1. **What are the potential benefits for the participant as well as benefits which may accrue to society in general, as a result of this study?** There is no direct benefit to the subject. There is a potential benefit to society for a better understanding of host factors in asthmatics that are likely to be critical in the pathogenesis of rhinovirus-induced asthma. In addition, the results of this study are expected to guide the development of new treatments designed to minimize the response to rhinovirus through a better understanding of the host characteristics that impart susceptibility to these infections.

2. Analyze the risk-benefit ratio.
The risks are minimal and there is a potential for benefit. As judged by the P.I. and co-investigators involved in this study, the risk-benefit ratio is acceptable.

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APPENDIX: Sponsor

Support Information

University of Virginia Asthma and Allergic Diseases Center, and the NIH (Grant #15494)

APPENDIX: Legal/Regulatory

Recruitment

The following procedures will be followed:

- *Finders fees will not be paid to an individual as they are not allowed by UVa Policy*

- *All recruitment materials will be approved by the IRB-HSR prior to use. The advertisements will be submitted to the IRB after the protocol has been approved.*
- *Only those individuals listed as personnel on this protocol will recruit and or conduct the consenting process with potential subjects.*

Clinical Privileges

The following procedures will be followed:

- *Investigators who are members of the clinical staff at the University of Virginia Medical Center must have been granted clinical privileges to perform specific clinical privileges whether those procedures are experimental or standard.*
- *The IRB cannot grant clinical privileges.*
- *Performing procedures which are outside the scope of the clinical privileges that have been granted may result in denial of insurance coverage should claims of negligence or malpractice arise.*
- *Personnel on this protocol will have the appropriate clinical privileges in place before performing any procedures required by this protocol.*
- *Contact the Clinical Staff Office- 924-5871 for further information.*

Sharing of Data/Specimens

Data and specimens collected under an IRB approved protocol are the property of the University of Virginia. You must have "permission" to share data/ specimens outside of UVa other than for a grant application and or publication. This "permission" may come in the form of a contract with the sponsor or a material transfer agreement (MTA) with others. A contract/ MTA is needed to share the data outside of UVa even if the data includes no HIPAA identifiers and no code that could link the data back to a HIPAA identifier.

- *No data will be shared outside of UVa, beyond using data for a grant application and or publication, without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.*
- *No specimens will be shared outside of UVa without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.*

Prisoners

If the original protocol/ IRB application stated that no prisoners would be enrolled in this study and subsequently a subject becomes a prisoner, the study team must notify the IRB immediately. The study team and IRB will need to determine if the subject will remain in the study. If the subject will remain in the study, the protocol will have to be re-reviewed with the input of a prisoner advocate. The prisoner advocate will also have to be involved in the review of future continuations, modifications or any other reporting such as protocol violations or adverse events.

Prisoner- Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.
For additional information see the OHRP website at http://www.hhs.gov/ohrp/policy/populations/index.html

APPENDIX: Drug Information

1 What is the drug name, manufacturer and IND# if available? Rhinovirus Strain 16 IND # 15162

2. If IND application has been submitted to the FDA, who is the Principal Investigator on the IND? Ronald Turner MD

3. What is the phase or stage of this study? NA, this is not a drug trial

APPENDIX: Pharmacy-Investigational Drugs/Biologics

1. What is the name of the investigational drug/biologic? Rhinovirus strain 16

2. Where will the subjects be seen for the administration/dispensing of the drug?
_Outpatient Unit: Hotel Room: Administration (inoculation) of RV-16 on Day 0.

3. What dose will be utilized in this study? 75-125 $TCID_{50}$ /0.25 ml in each nostril. Ten minutes later, the same dose will again be administered to each nostril.

4. What will be the frequency of dosing in this study? One time dose, as described above in #3, will be given to participants

5. What will be the duration of dosing in this study? NA, one time dose

6. What route of administration will be utilized? Intranasally

7. Will drug need to be prepared by the UVa Investigational Drug Service (IDS)?
NO- Drug (virus) will be prepared (i.e., at the proper $TCID_{50}$ dose) according standard established guidelines in Dr. Turner's laboratory.

8. Are there any special handling instructions mandated by the study (e.g. weighing hazardous materials)? No

9. Does the protocol provide provisions for dose titration, dose reductions, and or re-challenged (if drug is stopped), etc.? No

10. How will missed doses be handled? NA, one dose only

11. Will a comparator (active or placebo) be utilized in the protocol? No

12. Does this study involve research on a drug, biologic, supplement or food additive? Yes (RV-16 as described above).

►IF YES, is this study investigator initiated? Yes

13 Are you using a drug/supplement/ food additive in a manner not approved by the FDA? RV-16 is approved by the FDA for use in experimental rhinovirus challenges (BB-IND# 15162).

13a. Describe pertinent animal data that is available regarding the toxicity/safety of this drug. NA, none available

13b. Describe pertinent human data that is available regarding the toxicity/safety of this drug.

As noted above, the strain of RV that will be used is a pool of RV (strain 16) provided by Dr. Ronald Turner's laboratory at the University of Virginia. This pool has been extensively safety tested and has been approved for experimental challenge studies by the FDA (BB-IND # 15162).

13c. Have there been any human deaths associated with this drug? No

13d. In how many humans has this drug been used previously? In Dr. Turner's studies, 52 non-asthmatic adults (mostly UVA students) have been inoculated with this pool of rhinovirus (RV-16) during the past year. In our studies, we have previously inoculated 16 asthmatic subjects (using a similar study design and the same inclusion and exclusion criteria described for this study – see reference 8) with RV-16 before the FDA required that the pools of rhinovirus be produced under GMP conditions.

13e. If this protocol will be used in children describe any previous use of this drug with children of a similar age range. N/A

14. Do the following criteria apply?

_____ The investigation is intended to be reported to FDA as a well-controlled study in support of a new indication for use or intended to be used to support any other significant change in the labeling for the drug;

_____ If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is intended to support a significant change in the advertising for the product;

___**X**__ The investigation does involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

__X__ The investigation will be conducted in compliance with the requirements for institutional review set part in part 21CFR56 and with the requirements for informed consent set forth in part 21CFR50 ; and *This item must be checked.*

__**X**__ The investigation will be conducted in compliance with the requirements of 21CFR312.7 (Promotion and charging for investigational drugs)
This item must be checked.

15. Is this a post-marketing study? No

APPENDIX: Recruitment and Consenting

1. How do you plan to <u>identify</u> potential subjects

__X__Potential subjects will not be directly identified. They will respond to an advertisement such as a flyer, brochure : Screening protocol (IRB# 12656).

2. How will potential subjects be recruited?

__X__ Indirect contact (flyer, brochure, on-line emails, and student newspapers (e.g., the Cavalier Daily)

3. How will the consenting process take place? After subjects have completed the screening visits for this study (per IRB# 12656), the consent form will be reviewed with subjects who qualify and are interested in this study. The subjects will be able to ask any questions about their participation and the evaluation process. Copies of the consent form will be given to each subject screened.

4. Do you plan to ask the subjects to do anything for the study prior to signing a consent? No

5. **Do you need to perform a "dry run" of any procedure outlined in this protocol?** No

APPENDIX: Privacy Plan for Studies With Consent

1. Describe your plan to protect the identifiable data from improper use and disclosure.

__X__ Option # 2

Health information may be stored with HIPAA identifiers.
Specimens will be stored with or without HIPAA identifiers depending on security measures in place (see below).

Note: Health information obtained from subjects on questionnaires obtained during screening will be entered into a computerized database accessible only in the PI's laboratory (see also section 1a below). This information will be linked to stored specimens through the subject's study number, but will remain in strict confidence and will not be available to investigators other than the PI and his immediate staff who will be directly involved in the recruitment, screening and monitoring of subjects. No health information will be recorded directly on any samples or specimens.

1a. Will any of the data be stored electronically at UVa? yes

►IF YES, where will it be stored?
___X__ a Health Systems Computing Services (HS/CS) managed server that is configured to store data regulated by HIPAA,

1b. Will any of the data be stored in hard copy format at UVa *e.g.- on paper***?** Yes
►IF YES, where will it be stored?
___X__ case report forms will be stored in a secure area in the P.I.'s laboratory in MR-4 with limited access.

1c. The following procedures will also be followed

- Only investigators for this study and clinicians caring for the patient will have access to the data. They will each use a unique log-in ID and password that will keep confidential. Monitors and NIAID/DAIT staff at the NIH will also have access.
- If specimens are stored: The following security precautions will be implemented for specimens stored at UVa:
    - Specimens will be stored in a locked freezer/ or locked room

    ___X__Specimens will be stored with a code and no HIPAA identifiers
- Each investigator will sign the University's Electronic Access Agreement available at http://www.itc.virginia.edu/policy/form/eaa.pdf and forward the signed agreement to the appropriate department as instructed on the form.
  If you currently have access to clinical data it is likely that you have already signed this form. You are not required to sign it again.
- UVa Institutional Data Protection Standards will be followed http://itc.virginia.edu/security/dataprotection
- If identifiable data (*data with health information and HIPAA identifiers*) is transferred to any other location such as a desktop, laptop, memory stick, CD etc. the researcher must follow the ITC Policy "Electronic Storage of Highly Sensitive Data".http://itc.virginia.edu/security/highlysensitivedata/
- If the HIPAA identifiers and health information are combined on an additional computer off UVa premises, the researcher will follow the UVa "Guideline for Safeguards When Removing PHI Off- Premises for Work" https://www.healthsystem.virginia.edu/intranet/privacyoffice/Policies/PHI_Off_Premises.doc
- The data will be securely removed from the server, additional computer(s), and electronic media according to the University's Electronic Data Removal Policy. https://etg07.itc.virginia.edu/policy/policydisplay?id=IRB-004
- The data may not be analyzed for any other study without additional IRB approval

2. Describe your/central registry's plan to destroy the HIPAA identifiers at the earliest opportunity consistent with the conduct of the research.

___**X**__The HIPAA identifiers (except full dates and or address information if needed) will be destroyed as soon as all publications are complete.
This wording would allow the researcher to keep HIPAA identifiers until all queries/ request for additional information from publisher are addressed

3. **Do you confirm that you will not reuse the identifiable data (HIPAA identifiers or health information) or disclose any of this information to any other person or entity except as outlined in this protocol, except as required by law, for authorized oversight of the research study, or use it for other research unless approved by the IRB-HSR? Yes.**

This means that after the study is closed at UVa:

- ***You cannot contact the subject by any method (you cannot call them, send a letter, talk to them in person about the study, etc) without additional IRB approval***
- ***You cannot use the data for any research that is not already described in your IRB protocol without additional IRB approval (if you change your hypothesis you must modify your protocol)***
- ***You cannot share your research data with another researcher outside of your study team without additional IRB approval***

- ***Any health information with HIPAA identifiers will be shredded or discarded by using recycling bins for confidential material found in clinic settings. For large item disposal of confidential material contact Environmental Services at 2-4976 or University Recycling at 2-5050.***

Appendix 3: Asthma Control Test

Asthma Control Test™

This survey was designed to help you describe your asthma and how your asthma affects how you feel and what you are able to do. To complete it, please mark an ☒ in the one box that best describes your answer.

1. **In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

2. **During the past 4 weeks, how often have you had shortness of breath?**

More than once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all
☐1	☐2	☐3	☐4	☐5

3. **During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?**

4 or more nights a week	2 to 3 nights a week	Once a week	Once or Twice	Not at all
☐1	☐2	☐3	☐4	☐5

4. **During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as Albuterol, Ventolin®, Proventil®, Maxair® or Primatene Mist®)?**

3 or more times per day	1 or 2 times per day	2 or 3 times per week	Once a week or less	Not at all
☐1	☐2	☐3	☐4	☐5

5. **How would you rate your asthma control during the past 4 weeks?**

Not Controlled at all	Poorly Controlled	Somewhat Controlled	Well Controlled	Completely Controlled
☐1	☐2	☐3	☐4	☐5

To score the ACT

Each response to the 5 ACT questions has a point value from a 1 to 5 as shown on the form. To score the ACT, add up the point values for each response to all five questions.

If your total point value is 19 or below, your asthma may not be well-controlled. Be sure to talk to your healthcare professional about your asthma score.

Take this survey to your healthcare professional and talk about your asthma treatment plan.

TABLE A: HIPAA Identifiers (Limited Data Set)

1. Name
2. Postal address information, other than town or city, state, and zip code
3. Telephone numbers
4 Fax numbers
5. Electronic mail addresses
6. Social Security number
7. Medical Record number
8. Health plan beneficiary numbers
9. Account numbers
10. Certificate/license numbers
11. Vehicle identifiers and serial numbers, including license plate numbers
12. Device identifiers and serial numbers
13. Web Universal Resource Locators (URLs)
14. Internet Protocol (IP) address numbers
15. Biometric identifiers, including finger and voice prints
16. Full face photographic images and any comparable images
17. Any other unique identifying number, characteristic, code that is derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)