Inhaled Mometasone to Promote Reduction Of Vaso-occlusive Events Trial (IMPROVE Trial)
A feasibility study

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Supplement 1: Study protocol and schedule of protocol changes

- 12/24/2013: Protocol modified to add and remove study personnel
- February, 2014: First participant enrolled
- 3/11/2014: Minor changes to case report forms
- 6/30/2014: Add investigator signatures to case report forms
- 9/16/2014: Draw an additional 5-10 cc of blood at study entry and 8-weeks to performed cell-based assays of immune activation
- 5/11/2015: Clarify color of tubes for blood collection
- 9/18/2015: Change metrocard incentive to $11 from $10
- 11/18/2015:
    1. The medication adherence cutoff for inclusion in per-protocol analyses was changed from 80% to 70%
    2. The original protocol included non-adherent individuals in the intent to treat analyses but did not follow them after 8-weeks (i.e. after follow up questionnaires, clinical data, spirometry, eNO and blood were collected). The protocol was modified to continue following non-adherent individuals up to 16 weeks to evaluate strategies to improve medication adherence.
- October, 2016: Data collection completed

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1.3.2 Meeting Schedule

Advisory board meetings will occur quarterly

1.4 Data Safety and Monitoring Board

1.4.1 Personnel

MSSM Principal Monitor: Jeffrey Glassberg (PI)
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First Name: Jeffrey
Academic Title: Assistant Professor
Department: Emergency Medicine and Internal Medicine (Division of Hematology and Medical Oncology)
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1.4.2 Meeting Schedule

The DSMB will meet prior to subject enrollment and data collection and will meet at 6 month intervals thereafter

1.4.3 DSMB responsibilities

The DSMB will report Adverse Events (AEs) to the Mount Sinai Institutional Review Board, the funding I/C, the NIH Office of Biotechnology Activities (OBA), and the Food and Drug Administration (FDA) in accordance with Investigational New Drug (IND) regulations. The responsibilities of the DSMB will include: 1) overseeing the study's progress, 2) approving alterations or amendments to the study protocol, 3) monitoring safety and reviewing serious adverse events (SAE) which includes: death, intubation for acute chest syndrome, intensive care unit admission, or pulmonary infection, 4) overseeing data quality, 5) reviewing the interim analyses and recommending early trial cessation if indicated. The PI will be responsible for providing the DSMB with all necessary information.

1.5 Analysis Team

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2.1 Study organization and Responsibilities

2.2 Clinical coordinating center

The IMPROVE trial Clinical Coordinating Center (CCC) is directly responsible for the monitoring and oversight of all fiscal, regulatory, clinical and other general administration needed to centralize and coordinate the research endeavors of the IMPROVE trial. The CCC is located at the Icahn School of Medicine at Mount Sinai (ISMMS) and is led by the Study PI, Jeffrey A. Glassberg MD, MA. Under the PI supervision the senior research coordinator (SRC) will assist with the responsibilities of the CCC.

The responsibilities of the CCC will include:

- protocol and manual of operations development and amendments
- facilitating and monitoring protocol conduct
- overseeing regulatory compliance
- monitoring of adverse effects and events
- assuring quality control via site audits
- providing annual and quarterly reports on the progress of the IMPROVE Trial
- electing topics for investigation
- participating in the analysis and interpretation of data
- manuscript preparation and prioritization via the IMPROVE Trial Publication Policy
- plan and organize investigator and oversight meetings
- coordinate all NIH requirements related to the grant

2.3 Statistical coordinating center (SCC)

Collection and analysis of data generated for the IMPROVE trial will be coordinated by the PI and research coordinators (RCs) and will leverage the resources of the biostatistics,

epidemiology, and research design (BERD) program at ISMMS to monitor data collection. Responsibilities of the SCC will include:

- **Preparation of study documents**
  SCC staff will develop: Protocol, Manual of Operating Procedures (MOP), case report forms (CRFs), and QxQs (question by question), which give the details on answering the questions on every CRF). Materials given to participants (brochure/copy of consent form) will not mention the study acronym "IMPROVE" to avoid suggestive influence of the title.

- **Statistical design and sample size**
  SCC statisticians developed the statistical design for the study, including the primary outcome, sample size, randomization strategy, primary analysis strategy, and the complete analysis plan.

- **Training site personnel**
  SCC staff has have trained site personnel in all aspects of the study related to: details of the study protocol, data collection procedures, screening and randomization procedures, submitting forms to the SCC, laboratory preparation procedures, and responding to queries from the SCC. SCC staff will also monitor each site to assure that the site coordinators have completed the required training.

- **Receipt and processing of study forms at the SCC**
  SCC staff have designed and implemented the data management system for the study, including: electronic data entry, comprehensive editing of the data and preparation of protocol adherence aids, and data extraction for analyses related to research objectives. Data are submitted to the SCC through REDCap, a web-based data entry system. All hardcopy CRF's are maintained in a locked cabinet in a locked room. Once hardcopy enters this **storage facility**, it does not leave. Data are comprehensively edited once received at the SCC, prior to insertion into the main study database. Edit queries are resolved within a few days with the PI. The PI electronically signs off on all case report forms in REDCap before they are finalized. SCC staff also enforces patient confidentiality and privacy rules so that PHI data are not shared inappropriately and so that data are protected by multiple layers of security.

- **Monitoring study progress and data quality**
  SCC staff ensures that clinic site staff are properly trained, that performance of the required procedures are monitored, and that deviations from the protocol or from study norms are investigated. Routine site monitoring reports, including patient recruitment, performance of follow-up visits, and protocol compliance, will be produced at regular intervals. For spirometry, the SRC's past 10 PFT results will be reviewed to ensure reproducibility of results.

- **Quality assurance procedures**
  SCC staff will conduct quality assurance audits for every 5 participants enrolled in the study. In addition, quality assurance procedures and programs will be developed and implemented for laboratory determinations, for data collection, and for data entry.

- **Randomization**
  SCC staff have developed and implemented an adaptive, biased coin, covariate balanced randomization algorithm. The algorithm is implemented using a windows laptop running the program 'R' which will be carried on the IMPROVE research cart.

After screening for eligibility is complete, participants will be randomized. The Randomization algorithm will balance participants based on whether or not they take hydroxyurea and by the number of ED visits for pain during the preceding year (this variable will be trichotomized: 0-5, 6-10, 11-15).

- **Data and Safety Monitoring Board (DSMB) functions and reports**

  SCC staff will prepare reports for the DSMB and will respond to ad hoc queries from the DSMB. SCC staff developed the study monitoring plan, which indicates when interim monitoring of the efficacy outcomes will be performed, how adverse events will be reported, as well as the content of the DSMB reports. The DSMB reports will include tabulations and graphical presentation of administrative data (e.g., recruitment, compliance with therapy schedule, completion of follow-up procedures, and submission of data to the SCC), efficacy data (e.g., primary and secondary outcomes of the study, as required by the monitoring plan), and safety data (e.g., the occurrence of adverse events and serious adverse events).

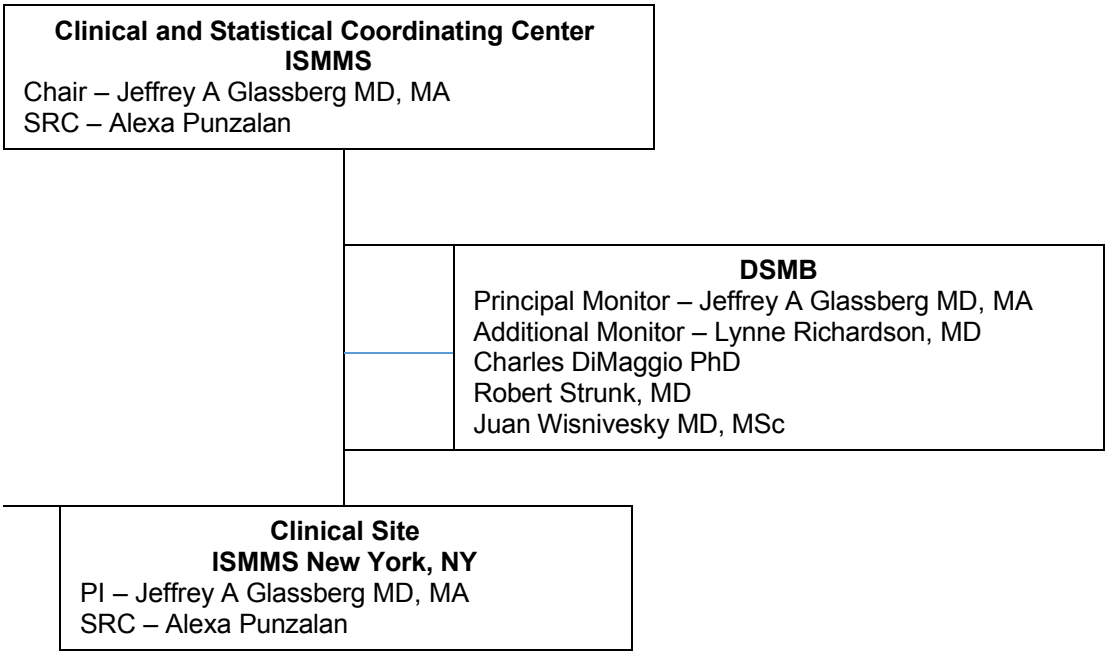
- **Statistical analysis plan**

  SCC staff developed the statistical analysis plan, which indicates, in detail, the main analysis for the primary outcome (including intention-to-treat analyses), secondary analyses, and analyses of the secondary and safety outcomes. In addition, the plan includes the frequency of DSMB reports, and how missing data will be handled.

- **Collaboration in study publications**

  SCC staff will collaborate in all study publications, providing statistical analysis, preparing the statistical methods and results sections of manuscripts, and preparing camera-ready tables and graphs. SCC staff will also participate in the development and review of abstracts for presentations and in the review of the statistical analysis for ancillary publications.

2.2.1 IMPROVE trial organizational chart



3.0 Study overview

We will conduct a randomized, double blind, placebo-controlled, feasibility study of mometasone furoate, an inhaled cortico-steroid (ICS), for 16 weeks in individuals with SCD and recurrent cough or wheezing who do not meet clinical criteria (derived specifically for individuals with SCD) for a diagnosis of asthma. Participants will be enrolled when they are pain free and have no acute respiratory symptoms. The sample size will be 45 participants, aged ≥15, with 2:1 allocation of drug to placebo. Feasibility will be determined by the proportion of individuals successfully randomized who maintain good adherence and complete at least 30 pain diaries vs. the total number enrolled.

4.1 Storage of study materials

4.2 The IMPROVE research cart

A mobile research cart will be maintained by the SRC. The research cart is equipped with a laptop, FVL machine (spirometry machine) with 3L syringe, disposable mouth pieces and nose plugs; mini centrifuge with micro tubes and pipettes. The research cart will also be stocked with study medication packets (closed envelopes which contain training materials and study medication or placebo), study binders (study logs, enrollment paperwork), and the NIOX MINO exhaled nitric oxide measuring device.

4.3 Study medication

As already approved by the ISMMS research pharmacy, study medication will be stored in Dr. Glassberg's office in a locked cabinet. Thermostat will be set at all times to maintain acceptable storage temperature (59-86 °F). Throughout the week, temperature and humidity (current readings as well as min and max for both) will be logged daily on the study medication temperature log sheet (CRF13) using a Fisher Scientific digital Traceable Thermometer/Clock/Humidity monitor. Over the weekend, min and max temperature and humidity will be logged on the Monday following. Min and max temperatures are stored after the memory is cleared (once each day). Dr. Glassberg packages, dispenses, and maintains accountability for all study medication is assisted by the unblinded RC in packaging and distribution.

Study packets for randomization will be made from sealable envelopes. Each packet will contain sufficient medication for 8 weeks (one 60-dose mometasone twisthaler or one placebo metered dose inhaler MDI). Packets containing active medication will include 'protocol orientation module A' (a document that has training and usage instructions for the mometasone twisthaler). Packets containing placebo will contain 'protocol orientation module B' (a document that has training and usage instructions for the placebo inhaler). Each packet will also include 60 pain diaries. Packets will then be sealed and labeled with a code. The code will indicate which treatment arm the packet corresponds to. The unblinded RC will have access to a master list that reveals the coding scheme, SRC and PI will not have access to this list.

In the event that Dr. Glassberg is not present during study recruitment/enrollment, licensed nurse practitioner Jena Simon will be present to oversee dispensation of study drug or placebo.

5.1 Recruitment, screening and eligibility procedures:

5.2 Screening potential participants in the ED

5.2.1 Overview

As stated in the protocol, in addition to clinic, potential participants will be identified in the ED.

In the ED, subjects will be identified by the PI or RC. The RC will ask the treating physician for permission to approach the patient. The RC will approach the patient in a private area conducive to private conversation (drawing the curtain in the ED). If the patient meets eligibility criteria (see 5.1.2) and expresses interest in participating in the study, the RC will take the patient's contact information (two phone numbers, address and email) to contact the patient at a later date to

discuss the study in greater detail and assess interest in participation. The patients contact information will be recorded in CRF 1 – Contact Information. The patient will be given information about the study (study brochure), and informed that there will be financial incentives for participating (metro-cards and gift cards at each visit).

5.2.2 Eligibility for screening ED patients

5.2.2.1 Inclusion criteria for screening

- Age 15 and older
- A history of SCD

5.2.2.2 Exclusion criteria for screening

- Unable to communicate
- Altered mental status
- Unstable vital signs
- The physician asks you not to approach the patient
- Pregnant

5.2.3 ED screening procedure

- .
- The RC will monitor the tracking board for indicators that a patient has SCD (chief complaint contains the word 'sickle' or chief compliant contains the word 'crisis')
- Once a patient has been identified, the RC will ask the treating physician for permission to approach the patient.
- The RC approaches patient in an area conducive to private conversation (private room or curtain pulled).
- RC explains that they are collecting contact information for people interested in participating in a clinical trial of a treatment for SCD.
- If the patient expresses interest, RC records contact information on CRF 1 – Contact Info.
- Completed CRF's are stored in the IMPROVE folder in a locked cabinet in Dr. Glassberg's office.
- The RC will enter CRF data into an encrypted Microsoft Access database and make weekly calls to prospective participants to arrange for an initial visit at the SCD clinic where the patient may be enrolled. In the event that the patient does not wish to follow in clinic but wants to participate in the study, a non-clinical visit in a private consultation room in the ED will be arranged.
- The RC will record de-identified information about each individual on CRF 10.
- The database will be destroyed when the study is complete.

5.3 Pre-screening and screening in clinic

5.3.1 Identification of eligible participants

When patients are greeted upon arrival to the SCD clinic, the RC will monitor the EPIC tracking board to identify patients who are above the age of 15 that have SCD. The RC will approach patients while they are in the waiting room to ask if they are interested in having a private discussion about a research study. Interested individuals will be brought to a private consultation area for screening and enrollment.

5.3.2 Eligibility

5.3.2.1 Inclusion criteria for randomization

- Age 15 and older
- Severe SCD phenotypes (Hb SS and Sβthalassemia^0)
- A positive response to cough/wheeze questions in CRF 3 – Screening Form.

5.3.2.2 Exclusion criteria for randomization

- Patient carries a physician diagnosis of asthma
- Patient is prescribed asthma medications
  (Note: short acting beta agonists will **not** be considered as part of the list of "asthma medications" that are grounds for exclusion from the study. Classes of asthma medications that will still constitute grounds for exclusion include: inhaled steroids, long acting beta agonists, leukotriene modifying drugs, and IgE targeting monoclonal antibody therapies)
- Patient is currently having a painful crisis (as defined by validated pain diary questions)
- Patient has acute respiratory symptoms
- known hypersensitivity to milk proteins
- meets criteria for our operational diagnosis of asthma (CRF 3 – Screening Form) will also be excluded.
- More than 15 ED visits for pain over the preceding 12 months
- Admitted or discharged from the hospital for SCD pain within the last 7 days
- Patient is pregnant or planning to become pregnant during the duration of the study.

5.3.3 Procedure

If the participant expresses interest in participating in the study, the RC will bring the patient to a private area and ask questions in CRF 3 – Screening Form. Completed CRF 3 forms will be destroyed once the patient's eligibility has been determined. If eligibility criteria are met on CRF 3 and the patient continues to express interest, the RC will then check EPIC for documentation that the patient has Hb SS or Sβthalassemia^0 and that the individual is not prescribed any asthma medications. If these criteria are met, the patient will be randomized.

5.3.4 Randomization and Enrollment

5.3.4.1 Overview

Individuals who meet inclusion/exclusion criteria will then be consented and randomized. The enrollment procedure is designed to maintain blinding of the participant, the PI and the senior RC. One RC will be unblinded (RC2) for purposes of introducing the study medication, training in proper use of the medication and refilling medication if the participant loses their medication.

5.3.4.2 Informed consent

Since an informed consent is a document required by law, this standard will require significant attention to all steps as set forth by good clinical practices. To ensure that patients' rights are protected and that all study participants receive, read, have explanation of and sign an informed consent prior to enrolling in any study or protocol, the following steps will be followed. The principal investigator or designee must:

1. Know all of the elements of informed consent
2. Explain to the patient/parent the importance of and reasons for obtaining informed consent
3. Provide the patient/parent a quiet, undisturbed area for him/her to read the informed consent.
4. If the patient/parent is unable to read, then read the consent to him/her slowly.
5. After the patient/parent completes the reading of the consent, provide adequate time for him/her to ask any study or consent related questions of the study doctor and or study nurse.

6. Document these questions and answers in the progress notes of the chart along with a notation that the consent was read and reviewed by the patient/parent, that the patient/parent was provided a signed copy, as well as the date and time the informed consent was signed..
7. The patient/parent should then sign and date the consent in all areas appropriate with **BLACK** ink only.
8. Witness the patient/parent signing the informed consent, then sign and date in the witness space of the consent.
9. Give the patient/parent a signed photocopy of the informed consent.
10. Retain the original signed informed consent document in the research chart with a copy in the patient's outpatient chart.
11. If the patient/parent must ever sign a revised/amended consent for this study, repeat this process. DO NOT dispose of any prior consent(s). They all remain a part of the record.

5.3.4.3 Baseline data collection

After the participant has completed the informed consent process, CRF 3 will be completed again to ensure the patient's eligibility to be a part of the study. Then the senior RC will administer CRF 4 the baseline data collection form.

5.3.4.4 Urine and serum collection and processing

The patient will then go to phlebotomy to have labs drawn as part of standard care for their visit. Research tubes will be supplied to the phlebotomist to be drawn in addition to standard care labs. A sterile cup will be provided for urine collection. Processing of samples will be done according to the following protocol. Samples are to be stored in the Annenberg building in Tom Moran's lab (Annenberg Building Floor 18 Room 18-08, 1468 Madison Avenue).

In clinic:
Collect blood in one gold top serum tube (~5mls blood), one paxgene tube (2.5ml blood), and two green top tubes (~5.5ml blood each). All samples will be sent for processing de-identified. The gold top tube is labeled with the date, patient ID and inverted 2x and stored in a portable ice chest for up to 6 hrs until transfer to lab for processing. The PAXgene tube blood will be labeled with by the study name, followed by the ID number starting with 7001 (and so on for consecutive participants) and V1 or V2 to designate the time point collected (V1at baseline and V2 at 8 Weeks). The PAXgene will be drawn vertically to allow blood to flow into the tube to exactly 2.5ml and inverted X8-10 after collection. The green top tubes will be labeled in the same manner as the PAXgene tube and inverted X5 after collection. The PAXgene tube can be kept at room temperature for up to 6 hours before transport at end of clinic day. The green top tube can be kept at room temperature for up to 30 minutes before transport to HIMC (Hess 5th Floor Rooms 310/313) for processing by HIMC staff.

For urine, instruct patient to sample clean catch in cup. Cup will be sealed, labeled, bagged and stored in a portable ice chest until processed.
In lab:
Blood: Spin at 2000 RPM, 5 mins, and aliquot serum into 4 labeled cryovials. Store at -80^{o}C.
Label as:
Date Patient ID
Serum (or Urine)
PI: J. Glassberg, MD

Urine: Transfer to vacutainer to centrifuge as above.
Aliquot in labeled cryovials and store at -80.

(For HIMC SOP see appendix)

5.3.4.5 Pulmonary Function Testing

Steps for PFT Testing

Summary: Calibrate the device before testing on patients for the day.

1. Calibration – typically once a day
    a. Go to Calibration
    b. Run QC Spirometry
        i. Connect the 3-L syringe to the blue adaptor tube. Connect the other end of the blue tube to the narrower side of the mouthpiece, which then connects to the FVL. Make sure the syringe is closed. Click Done.
        ii. The device will check for zero flow. Do not pump the syringe at this time.
        iii. Following the instructions, pull the syringe to fill with air, then push at different flow rates:
            1. 2 times at the low flow rate target, at least 1 time at each of the higher flow rates
    c. Troubleshooting Failed ATS (failing QC)
        i. Redo QC Spirometry.
        ii. If failed again, click the red button at the lower left corner of the calibration home screen (diagnostics and device configuration).
        iii. Go to Create New Span Factor → Span pneumotach F/V → With syringe connected, aim for targets
        iv. Once ATS passed, click the red button (diagnostics and device configuration) and perform QC again.
            1. If QC still fails, then recalibrate by building a new table under diagnostics and device configuration.
2. Run Test
    a. Create a patient
        i. Go to New Patient at the right of the Patients home screen.
        ii. Fill in Identification and Information
        iii. Save.
        iv. For each test, fill in Biometrics, Smoking, Referral, etc.
        v. Patients for the day can be found in the scroll down at the top of the program. Patients can also be searched under Find at the top or under Patients.
    b. Go to Run Test on the left or on the middle right of the patients home screen.
        i. Enter Environmental Data (default values may be okay depending on study)
        ii. Make sure patient's mouthpiece is attached to the FVL.
        iii. Go to Start Pre Effort and allow device to verify zero flow. Make sure patient is not breathing into mouthpiece
        iv. Ask patient to wear nose clip and to insert the mouthpiece, creating an airtight seal with the mouth and resting the tongue under the opening of the mouthpiece.
        v. After at least two tidal waves of normal breathing, tell the patient to take a deep breath on the next inhale and to blast everything out as hard and fast as possible.
        vi. Encourage the patient to continue pushing out air for at least 6 seconds. 8 seconds recommended. Watch the Forced Expiratory Time (FET) dial to countdown.
        vii. Collect at least three good tests
    c. Administer 2 puffs albuterol via metered dose inhaler
    d. Repeat test using post bronchodilator fields

5.3.4.6 Measurement of Exhaled Nitric Oxide using NIOX Mino

1. Run Test
    a. Empty Lungs
    b. Inhale deeply through the disposable filter
    c. Make a seal with mouth on mouthpiece
    d. Exhale through the disposable filter for ten seconds or longer when machine beeps
    e. View the results on the screen

5.3.4.7 Randomization

Randomization will use an adaptive biased coin algorithm using the software program R as the user interface. After CRF 4 is complete the SRC will leave the room and the second RC (referred to as RC2 from this point forward) will enter to perform the randomization process.

RC2 will enter the room with the IMPROVE research cart and open the study laptop. RC2 will open R and load the randomization algorithm program. The program will prompt RC2 to enter a) whether or not the patient takes hydroxyurea and b) how many ED visits or hospital admissions for pain the patient has had over the preceeding year c) the patients unique study identification number. The randomization algorithm will then notify RC2 which treatment arm the patient has been assigned to using a letter code (treatment arm A or B). Labeled study packets will be kept in the research cart and RC2 will hand the participant an appropriately labeled packet. At this time RC2 and the participant will open the packet together to review the study materials. The steps will be as follows:

1. Inhaler training – RC2 will train the participant in proper use of the inhaled medication including inhalation technique dosing intervals, what to do about missed doses.
2. Pain diary training – RC2 will train the participant regarding proper use of the pain diaries.
3. Contact information – RC2 will instruct the participant about how to contact study personnel in the event that the participant loses medication, has questions, suffers adverse events.

Once the training is complete, the participant will be instructed to put away their medication so that other study personnel do not see it. RC2 will leave the room.

The SRC will then enter the room and explain the schedule of financial incentives. The participant will be given a $30 gift card and a $11 metro card. A second follow up visit will be scheduled for 8 weeks from the current date. At this point the participant will be released and any other medical care will resume.

6.1 Telephone follow up (week 2)

6.2 Overview

A follow up telephone call will be conducted 2 weeks after the patient is enrolled in the study. The goal of this phone call is to identify adverse events, to assess medication adherence, and pregnancy surveillance in female patients. Patients who become pregnant during the study will be asked to stop taking the medication and they will be withdrawn from the study. The phone script and event questionnaire (to assess for adverse events) is contained in CRF 2 – Adverse Events Form.

7.1 Telephone follow up (week 4)

7.2 Overview

A follow up telephone call will be conducted 4 weeks after the patient is enrolled in the study. The goal of this phone call is to identify adverse events, to assess medication adherence, and pregnancy surveillance in female patients. Patients who become pregnant during the study will be asked to stop taking the medication and they will be withdrawn from the study. The phone script and event questionnaire (to assess for adverse events) is contained in CRF 2 – Adverse Events Form.

8.1 In-person follow up (week 8)

8.2 Overview

The participant will be scheduled to return for an in-person follow up 8 weeks after study initiation. It is likely that the participant will also need to visit the clinic for standard care. If no visit is indicated, the visit will be conducted for purely research purposes without billing for medical care or utilization of any institutional services.

8.3 Intake

The participant will be greeted by the SRC when they arrive at the clinic. Prior to phlebotomy the participant will be taken to a private area for data collection.

8.4 Medication Refills

If the participant meets criteria to remain in the study (see 7.2) RC2 will refill the participant's medication. RC2 will go over with the patient inhaler technique and dosing schedule to confirm that the participant is using the medication properly. Once medication has been given to the participant, they will be instructed to put their medication away.

8.5 Adherence Status Check

CRF 8 – 8 Week Adherence Status check identifies if the participant has remained adherent to study guidelines (at least 70% of doses and 15 pain diaries). CRF 8 – 8 Week Adherence Status will be filled out by RC2 as this requires that the RC visualize study medication in an unblinded fashion. If at any time the participant falls below the cut-off for medication or diaries, they will be re-instructed to bring them back to compliance.

8.6 Data collection

8.6.1 Questionnaire

The 8-week questionnaire will include data regarding respiratory symptoms, medication adherence, health-related quality of life, adverse events, side effects, and pregnancy surveillance in female patients. Patients who become pregnant during the study will be asked to stop taking the medication and they will be withdrawn from the study. Once it is confirmed by RC2 that the participant will remain in the study, CRF 5 – 8 Week Data Collection will be administered by the SRC.

8.6.2 Serum collection

Serum collection will follow the same processing procedures as 5.2.4.4. When participants in clinic are having blood drawn as part of standard care, research tubes will be given to the phlebotomist to be drawn in addition to clinical labs.

8.6.3 Pulmonary function testing

Pulmonary function testing will be done according to the same procedure as 5.2.4.5. Data will be recorded in CRF 5a – Spirometry and Exhaled NO2.

8.6.4 Exhaled Nitric Oxide

Exhaled nitric oxide will be measured according to the same procedure as 5.2.4.6. Results will be recorded in CRF 5a – Spirometry and Exhaled NO2.

8.7 Pain Diary Processing

Completed pain diaries will be reviewed for missing data and accuracy (missing dates, ID number) and then brought to the SCC storage facility for processing. Complete pain diary entries are constituted by completion of questions 3 and 4. Diary entries with missing answers to question 3 and 4 will be considered incomplete. Diaries will be stored securely with other CRF's.

8.8 Financial Incentives/additional pain diaries

Once data collection is complete, the SRC will give the participant a second packet of pain diaries to complete over the subsequent 8 weeks. The SRC will also give the patient their financial incentives based on the number of diaries properly filled out as indicated by the schedule below (table 1).

Table 1
Timeline of financial incentives

	Visit 1 – Baseline Week 0	Visit 2 eek 8	Visit 3- end W e	Obs rvation† ek 20
Participants expected	56	50	45	45
Gift Card ($30) -	X	X	X	X
Metro card ($11) – travel costs	X	X	X	X
Gift card for completion of pain diaries		< 15 diaries – 0$ 15-25 – 10$ (50%) 26-50 – 20$ (40%) 51-56 – 30$ (10%)	< 15 diaries – 0$ 15-25 – 30$ (50%) 26-50 – 60$ (40%) 51-56 – 90$ (10%)	< 15 diaries – 0$ 15-25 – $ (80%) 26-28 – $ (10%)
†Observational follow up period will continue for 4 weeks after study completion to measure adverse events, changes in pain and the proportion who choose to continue ICS.				

8.9 Discharge and follow up arrangements

After completion of data collection, a follow up visit will be scheduled for 8 weeks from the current date (16 weeks after study initiation). At this point the participant will be released and any other medical care will resume.

9.1 Telephone follow up (week 12)

9.2 Overview

A follow up telephone call will be conducted 12 weeks after the patient is enrolled in the study. The goal of this phone call is to identify adverse events,to assess medication adherence, and pregnancy surveillance in female patients. Patients who become pregnant during the study will be asked to stop taking the medication and they will be withdrawn from the study. The phone script and event questionnaire (to assess for adverse events) is contained in CRF 2 – Adverse Events.

10.0 End of study visit (week 16)

10.1 Overview

The participant will return for a second in-person visit 16 weeks after study initiation. During this visit, medication administration for the purposes of research will be stopped. If the patient believes that the medication is helping them, then the medication may be continued if the patient's primary doctor agrees to this course of care. The primary doctor will be responsible for writing prescriptions for inhaled steroids or for arranging subspecialty follow up with a pulmonologist.

10.2 Intake

The participant will be greeted by the SRC when they arrive at the clinic. Prior to phlebotomy the participant will be taken to a private area for data collection.

10.3 Collection of study medication

RC2 will collect the participants study medication once they are brought to a private area. CRF 9 – 16 Adherence Status will be filled out by RC2 to document medication adherence. If at any time the participant falls below the cut-off for medication or diaries, they will be re-instructed to bring them back to compliance.

10.4 Procedures for individuals who wish to continue study medication

If a participant expresses a desire to continue the study medication long term, the first step will be to determine whether the participant received placebo or drug. RC2 will reveal which treatment arm the participant was in. Patients who received placebo will be informed that they were not given medication and that there is no indication to initiate inhaled steroids at this point. For patients who received mometasone, the PI will contact the participant's treating physician to discuss the case. Initiating long term inhaled corticosteroids will be at the treating physician's discretion.

10.5 Data collection

The 16-week questionnaire will include data regarding respiratory symptoms, medication adherence, health-related quality of life, adverse events, side effects, and pregnancy surveillance in female patients. Patients who become pregnant during the study will be asked to stop taking the medication and they will be withdrawn from the study. Once it is confirmed by RC2 that the participant will remain in the study, CRF 6 – End of Study Questionnaire will be administered by the SRC.

10.6 Pain Diary Processing

Completed pain diaries will be reviewed for missing data and accuracy (missing dates, ID number) and then brought to the SCC storage facility for processing. Diaries will be stored securely with other CRF's.

10.7 Financial Incentives/additional pain diaries

Once data collection is complete, the SRC will give the participant a new packet of pain diaries to complete over the subsequent 4 weeks. The SRC will also give the patient their financial incentives based on the number of diaries properly filled out as indicated by table 1.

10.8 Discharge and follow up arrangements

After completion of data collection, a follow up visit will be scheduled for 4 weeks from the current date (20 weeks after study initiation). At this point the participant will be released and any other medical care will resume.

11.0 Post-protocol observation period visit (week 20)

11.1 Overview

The participant will return for a final, post-protocol visit 4 weeks after completion of the study. The goal of this visit will be to assess for adverse events in individuals who discontinued inhaled corticosteroids. Participants who noted substantial worsening of symptoms (SCD or breathing related) will be given the opportunity to have research staff speak with their primary treating physician regarding initiation of long term use of inhaled steroids. The primary doctor will be responsible for writing prescriptions for inhaled steroids or for arranging subspecialty follow up with a pulmonologist.

11.2 Intake

The participant will be greeted by the SRC when they arrive at the clinic. Prior to phlebotomy the participant will be taken to a private area for data collection.

11.3 Procedures for individuals who wish to continue study medication

If a participant expresses a desire to continue the study medication long term, the first step will be to determine whether the participant received placebo or drug. RC2 will reveal which treatment arm the participant was in. Patients who received placebo will be informed that they were not given medication and that there is no indication to initiate inhaled steroids at this point. For patients who received mometasone, the PI will contact the participant's treating physician to discuss the case. Initiating long term inhaled corticosteroids will be at the treating physician's discretion.

11.4 Data collection

The 20-week questionnaire will include data regarding respiratory symptoms, pain and stiffness modules of health-related quality of life,adverse events, and pregnancy surveillance in female patients. Patients who become pregnant during the study will be asked to stop taking the medication and they will be withdrawn from the study. The questionnaire will also ask for updated contact information for the participant. CRF 7 – Post Protocol Questionnaire will be administered by the SRC or RC2.

11.5 Pain Diary Processing

Completed pain diaries will be reviewed for missing data and accuracy (missing dates, ID number) and then brought to the SCC storage facility for processing. Diaries will be stored securely with other CRF's.

11.6 Financial Incentives

Once data collection is complete, the SRC will give the patient their financial incentives based on the number of diaries properly filled out as indicated by table 1.

11.7 Discharge and follow up arrangements

After completion of data collection, the participant will be informed that their participation in the study is complete. At this point the participant will be released and any other medical care will resume.

12.0 Procedures for loss of study medication

Participants will be given contact information for the SRC and Dr. Glassberg at entry into the study.

In the event that a participant loses their study medication they will be instructed to contact the SRC. Loss of study medication may also be identified at follow up phone calls. In this event, the SRC will instruct RC2 to determine which treatment arm the participant is in, obtain an additional inhaler and arrange to give the participant a replacement inhaler. RC2 will record on CRF 11 the date of replacement, and the estimated number of doses used before the initial inhaler was lost.

13.1 Data management procedures

13.2 Study logs

All study logs are maintained by the SRC with regular monitoring by the PI.

13.3 Case report forms

All CRF's are maintained by the SRC with regular monitoring by the PI. Any changes to CRFs will require a modification of the IRB protocol.

14.1 Data Analyses

14.2 Primary and Secondary Outcomes: The primary outcome for the study is feasibility. **Feasibility** will be determined by calculating the proportion of randomized patients who complete follow up and a minimum of 30 pain diaries (as was required in the PiSCES study)[73] with good adherence to the study medication vs. the number enrolled. Other findings relevant to feasibility will include retention rate (% who complete the study), points of attrition, recruitment rates (# approached vs. # enrolled) and adherence (via dosage counters - use of more than 70% of doses) as a function of recruitment site (clinic vs. ED).

14.3 Potential outcomes for a definitive multi-center trial. We will collect outcome data which will yield imprecise estimates of effect on patient-oriented vaso-occlusive, respiratory and safety outcomes. Vaso-occlusion will be measured in 5 ways 1) daily pain diaries (see exploration of potential definitive outcomes), 2) ED visits for pain; 3) hospital admissions (or observation unit stays) for pain 4) hospital admissions for ACS and 5) Health-related quality of life (change in ASCQ-Me score). While a primary clinical outcome was not specified, sample size calculation were based on detecting a difference in pain diary data (see data analysis). Respiratory outcomes will include self-reports of symptoms from the SAC survey. Safety outcomes include infections, adverse reactions, pain, avascular necrosis, stroke and intracranial hemorrhage. Data Collection and management for

aim 1: Data will be collected by the PI or RC in the manner described in 'subject identification and recruitment' above. All ED screening forms (CRF 1) will be kept in a file in a locked cabinet in the PI's office. Relevant laboratory data will be extracted from the medical record onto case report forms (see CRFs). Data will then be manually entered into database REDCap database. Hardcopies will be maintained in a locked file cabinet in the PI's office. Identifiable data will be kept in either the REDCap database or on harcopy locked in a file cabinet in the PI's office. Hardcopy with identifiable data will never leave the PI's office. All data that is shared outside of the PI's office (i.e with statistician) will be stripped of identifiers and participants will be identified only by a unique ID number.

14.4 Aim 2: Primary and Secondary Outcomes: This aim will assess changes in pulmonary inflammation and vascular injury with ICS therapy. The primary outcomes for the trial will be **change in eNO (pulmonary inflammation) and sVCAM (vascular injury)** level 8 weeks after randomization. Secondary outcomes will be change in reticulocyte index, change in FEV_1/FVC ratio (expressed as percent predicted) and change in other key biomarkers.

14.5 Data Analysis: *Preliminary analyses* - Descriptive analyses for all socio-demographic and clinical variables will be performed. Preliminary data analyses will focus on examination of the distributional characteristics of measures used in the study. In this step, decisions will be made regarding possible transformations that might be required to meet the assumptions of the statistical tests that will be employed. Baseline values for individuals in each randomization assignment will be compared using t-tests, chi-square and non-parametric tests when appropriate. For outcomes that may be used in a definitive trial, univariate analyses will be performed first followed by stratified analyses with potential confounders (variables known or suspected to have associations with the frequency of painful episodes including age, gender, genotype, baseline hemoglobin, leukocyte count, and fetal hemoglobin percent). Potential confounders with p-value less than 0.2 will be included in parsimonious models.

14.6 *Primary* analyses: The primary outcome, **feasibility** as well as retention/recruitment rates, attrition points and adherence will be expressed for those enrolled from the ED and the hematology clinic. Feasibility measures will be compared between those enrolled in the ED vs. clinic using χ^2 statistics. Adherence (defined as use of greater than 70% of indicated doses by dosage counter) will be compared to the previously validated MARS-A score cutoff of 4.5 with a χ^2 statistic to validate the use of MARS-A in SCD.

14.7 Exploration of **potential definitive outcomes:** For the pain diary self-report measures of pain a linear mixed repeated measures model will be implemented with the SAS procedure MIXED to compare mometasone and placebo. The nesting variable will be participant ID number; main effects will be time, treatment group and interaction of time by treatment group. This will allow for variability in the number of diaries completed and variable effects of ICS over time (expected to increase with duration of treatment). For the measures of vaso-occlusion with poisson distributions (frequency of hospital visits for pain, ED visits for pain and hospital visits for acute chest syndrome), multivariable negative binomial regressions will be performed to estimate rate ratios based on treatment assignment. We expect self-report HRQL measures (change in ASCQ-Me score) to be approximately normally distributed. Pain diary data will be expressed in terms of several summary measures as described I the PiSCES project including number of days in 'crisis', number of pain days, number of days requiring opiate use and mean pain severity.[71] Categorical summary measures will be compared with χ^2 statistic, continuous variables will be compared with t-tests or non-parametric tests as appropriate. Additionally, for potential patient-oriented outcomes, a series of Bayesian analyses will be performed. For normally distributed variables (i.e. ASCQ-Me pain domains) a posterior distribution will be estimated for the difference between treatment groups. This will be achieved by using a non-informative Gaussian distribution as the conjugate prior. Markov-chain monte carlo simulation will be used to obtain random samples from the posterior distributions of each treatment group such that the distribution of the difference between treatments can be estimated. The same procedure will be used for other patient-oriented outcomes. For poisson distributed outcomes (ED visits, hospital admissions) a gamma prior will be

used, for binomial outcomes we will use a beta prior. All Bayesian analyses will be performed in R. Bayesian analyses will also be used to estimate adverse events if any occur.

14.8 Sample Size Analysis: While the primary outcome of the study is feasibility, we did perform a sample size analysis to estimate measures of treatment effectiveness based on mean pain scores from pain diaries. It is unlikely that average correlation before and after treatment would be equal to 0.5 because we expect the treatment group's pain scores to decline while the control group remains about the same. For the proposed sample sizes, to detect a difference in mean pain score of 1 point for ICS vs placebo if the correlation is 0.40, power = 0.74, for a correlation of 0.30, power = 0.77, and for 0.20, power = 0.80.[84]

14.9 Data Analysis: Preliminary analyses will be performed as described in Aim 1. For the primary outcome eNO and sVCAM

170,251.61	-175,849.40

14.10 , change scores will be created by subtracting levels drawn at 8 weeks from those drawn at study entry. These change scores will be analyzed using a t-test with treatment group as the explanatory variable. Change scores and t-tests will be calculated for the secondary outcomes (sVCAM, reticulocyte index, FEV_1/FVC, other biomarkers) in the same manner. Additional Bayesian analyses will also be performed to estimate changes in biomarkers using the same techniques described in "exploration of potential definitive outcomes" above.

14.11 Sample Size Analysis: Using a correlation of 0.5 between pre and post-treatment eNO levels, the proposed sample size will have 80% power to detect a difference of 5 ppb between mometasone and placebo. The study will have 90% power to detect a difference of 5.8 ppb.[101] Thus we will have adequate power to detect even small reductions in levels of eNO across treatments.

14.12 Interim Data Analysis: Interim data analysis will be done after the first 20 participants have been enrolled. Interim analysis will use the same analytical analyses above.

15.1 Schedule of oversight procedures

15.2 DSMB meetings

In accordance with NIH policy, a Data Safety Monitoring Board (DSMB) will be constituted. The DSMB will consist of members of the advisory committee: Dr. Strunk, Dr. Wisnivesky, and Dr. DiMaggio. The DSMB will report Adverse Events (AEs) to the Mount Sinai Institutional Review Board, the funding I/C, the NIH Office of Biotechnology Activities (OBA), and the Food and Drug Administration (FDA) in accordance with Investigational New Drug (IND) regulations. The DSMB will meet prior to subject enrollment and data collection and will meet at 6 month intervals thereafter to review study progress and monitor patient safety. The responsibilities of the DSMB will include: 1) overseeing the study's progress, 2) approving alterations or amendments to the study protocol, 3) monitoring safety and reviewing serious adverse events (SAE), 4) overseeing data quality, 5) reviewing the interim analyses and recommending early trial cessation if indicated. The PI will be responsible for providing the DSMB with all necessary information.

As per IRB policies, all SAEs regardless of relationship to the research will be reported to the IRB within 24 hours and will be listed in the annual IRB application for continuation or termination of the research. All expected non-serious adverse events that occur at a greater frequency or severity than anticipated and all unexpected non-serious adverse events will be reported to the IRB within 15 working days and summarized annually to the IRB in the continuation or termination applications. Reports of adverse events will also be reviewed by the PI and the primary mentor at their weekly meeting. Questions and concerns will be discussed with the DSMB during scheduled meetings or in between meetings if a more serious concern arises.

15.3 FDA annual reports

The IND for this study is held by Dr. Glassberg. Dr. Glassberg is responsible for maintaining compliance with FDCA (21 U.S.C. §§ 301 et. Seq.) as well as implementing regulations [title 21 of the code of federal regulations (CFR)]. All reporting requirements described in the IND will be med.

16.0 Provisions for research related injury

The physicians on the research team and the DSMB will address any adverse events or refer the study participants for specialized treatment, if appropriate. Adverse events will be recorded in CRF 2 and deaths will be recorded on CRF 12. Published data suggest that inhaled mometasone at this dose will not cause serious adverse events in this population. If a study participant develops an adverse event, decisions will be made on a case-by-case basis to determine if the patient should be withdrawn from the study.

As discussed above, there are risks associated with participation in the proposed project. As detailed in HRP 503, risks associated with participation are minimal and all efforts will be made to avoid these risks. Staff will be trained to minimize risks associated with phlebotomy and other collection procedures. With regard to the risks associated with inhaled mometasone, the risks of adverse events are extremely low with the proposed dose of study medication. Participants will be followed very closely to assess for adverse events (see Data Safety and Monitoring Plan). For individuals who benefit from ICS, all efforts will be made to make ICS available via prescriptions from the participant's primary provider after conclusion of the study. Individuals randomized to placebo will be contacted after study data are analyzed to inform them if ICS are beneficial. The PI will also offer to contact primary providers for patients randomized to placebo if they would like to begin treatment with ICS.

If at any time, a subject expresses verbal or nonverbal unwillingness to participate, the subject will be withdrawn from the study.

17.0 Procedures for study withdrawal

Any participant experiencing serious adverse events will be considered for exclusion after adjudication by the DSMB.

18.1

Appendix 3 – HIMC SOPs

Supplement 2: Screening and eligibility form

(Affix Label Here) Participant ID: _____	Date Form Filled Out: __ __ __ __ __ __ __ __ day month year	IMPROVE Inhaled Mometasone to Promote Reduction of Vaso-occlusive Events

Screening questionnaire to determine eligibility

Group 1

1. Does the participant's chest ever sound wheezy or whistling occasionally even without having a cold?

   ☐ Yes ☐ No

2. Has the participant ever had an attack of wheezing that has caused him/her to be short of breath?

   ☐ Yes ☐ No

3. Does this participant ever get attacks of wheezing after he/she has been playing hard or exercising?

   ☐ Yes ☐ No

Group 2

4. Has a doctor ever said the (BIOLOGICAL) mother of the participant had asthma?

   ☐ Yes ☐ No

5. Has a doctor ever said the (BIOLOGICAL) father of the participant had asthma?

   ☐ Yes ☐ No

Group 3

6. Has a doctor ever said that the participant has asthma?

   ☐ Yes ☐ No

7. Does the participant still have asthma?

   ☐ Yes ☐ No

8. Does the participant take any asthma medications?

   ☐ Yes ☐ No

Group 4

9. During the past 2 months, how often did the participant awaken from sleep because of cough or wheeze?
   - ☐ Never
   - ☐ Almost every night
   - ☐ At least once a week but not nightly
   - ☐ At least once a month but not weekly
   - ☐ At least once but not monthly

10. During the past 2 months, how often did the participant cough or wheeze during or after exercise?
   - ☐ Never
   - ☐ Almost every night
   - ☐ At least once a week but not nightly
   - ☐ At least once a month but not weekly
   - ☐ At least once but not monthly

11. During the past 2 months, how often did the participant cough or wheeze during the day unrelated to exercise?
   - ☐ Never
   - ☐ Almost every night
   - ☐ At least once a week but not nightly
   - ☐ At least once a month but not weekly
   - ☐ At least once but not monthly

GROUP 5

12. Is the patient currently experiencing a sickle cell pain crisis?
   - ☐ Yes
   - ☐ No

13. Over the past 12 months how many ED or hospital visits did you have for sickle cell pain?
   - ☐ 0-5
   - ☐ 6-10
   - ☐ 11-15
   - ☐ >15 (EXCLUDE)

14. Have you been admitted or discharged from the hospital in the past 7 days?
   - ☐ Yes
   - ☐ No

15. FEMALE PATIENTS ONLY: Is the patient Pregnant?
   - ☐ Yes
   - ☐ No

Inclusion/Exclusion Scheme:
Participants are eligible if they do not answer 'never' to all questions in group 4

Exclude Participants if

a. They answer yes to all 3 questions in group 1
b. They answer yes to 2 questions in group 1 and 1 or more questions in group 2
c. They answer yes to questions 6 and 7 or questions 6 and 8
d. They answer yes to questions 12 , 14, 15 and >15 for question 13 in group 5

Investigator Approval of Eligibility:_____ Date: _____

Supplement 3: Inhaler training and adherence modules

(Affix Label Here) Participant ID: _	Date Form Filled Out: __ __ __ __ __ __ __ __ day month year	Inhaled Mometasone to Promote Reduction of Vaso-occlusive Events

Protocol Orientation Module A

If you lose your medication

Contact study staff immediately:

[redacted]

Pain diaries

Pain diaries are included in your package. Try to fill out a pain diary every day. If you miss a day that's ok. You must fill out at least 30 diaries to stay in the study.

Your medicine

This package contains your medicine for this study. Take one puff of the medicine every day. The research coordinator will teach you how to use the inhaler.

(Affix Label Here) Participant ID: _	Date Form Filled Out: _ _ __ _ _ _ _ __ __ day month year	Inhaled Mometasone to Promote Reduction of Vaso-occlusive Events

Protocol Orientation Module: Adapted from "BREATHE EASIER: AN ADULT ASTHMA EDUCATION PROGRAM" and Mometasone Package Insert

"Breathe Easier"
Developed by the American Institutes for Research and
the Kaiser-Permanente Medical Group
National Heart, Lung, and Blood Institute
National Institutes of Health
National Asthma Education and Prevention Program

FOR ORAL INHALATION ONLY

Please read this leaflet carefully before taking this medication
This leaflet does not contain the complete information about this medication. If you have any questions about mometasone inhalation ask your health care provider or pharmacist.

IMPORTANT POINTS TO REMEMBER

- Use this medication regularly and at the same time each day, as prescribed by your health care provider. You or your child may not get the most benefit for 1 to 2 weeks or longer after starting the medication. If you or your child's symptoms do not improve in that time frame or if your condition gets worse, contact your health care provider.
- The cap is needed to use the TWISTHALER. Do not twist the mouthpiece with your hand. When the cap is removed from the TWISTHALER, the dose counter will count down by one, and show the number of doses available after this use.
- The inhaler delivers your medicine as a very fine powder that **you or your child may not taste, smell, or feel**. Do not take or give extra doses unless your health care provider has told you to.
- It is important to replace the cap after each inhalation to protect the inhaler from moisture.
- Do not use the inhaler if you notice that it is not working correctly. Take it to your health care provider or pharmacist.

UNDERSTANDING YOUR MEDICATIONS

MATERIALS FOR SESSION:

• twisthalers

As part of this study you will be given an inhaler. This inhaler may contain placebo (no medication) or it may contain a medicine called mometasone. Mometasone is part of a class of medications called corticosteroids.

This is a medication taken regularly every day even when you don't have any symptoms

Although they have a similar name, these steroids are very different from the anabolic steroids that have been in the news in recent years because of their ill-advised use by athletes to increase muscle mass.

Corticosteroids are:

• Anti-inflammatory-Corticosteroids are a very effective anti-inflammatory medication and help reduce or prevent edema and excess mucus in the bronchial tubes.

• Have delayed action-· Corticosteroids do not relax the muscles around the bronchial tubes and will not open the airways immediately as do the bronchodilators. For this reason, they may not *seem* to have any effects. However, over time they can be very beneficial in reducing inflammation.

Inhaled corticosteroids have very few side effects, when used in moderate doses, but they must be taken regularly to be effective.

Possible side effects: an unpleasant taste and gastrointestinal symptoms (e.g., nausea). They may cause a yeast infection ("thrush") in the mouth or bother the upper airways and cause coughing.

Proper Inhaler Use (10 minutes)

The medication that we have been discussing is administered by aerosol inhaler, and proper inhaler use is very important for maximum benefit. If inhalers are not used correctly, the medications don't help much because they can't get all the way down into the narrow airways. Many times patients stop using their inhalers (or, on the other hand, overuse their inhalers) because they think the medicine is not working. In reality, it's not working only because they aren't using it right.

Go over steps while you demonstrate correct usage.

Instruct participants to take one puff per day

Let's take a few minutes to review inhaler use and make sure each of you is using the best technique.

How To Use YOUR INHALER

HOW TO USE ASMANEX TWISTHALER OR GIVE TO YOUR CHILD

- **Remove the ASMANEX TWISTHALER from its foil pouch and write the date on the cap label.**
- **Throw away the inhaler 45 days after this date or when the dose counter reads "00", indicating the final dose has been inhaled, whichever comes first.**
- **Follow steps 1 and 2 below each time you inhale a dose from your ASMANEX TWISTHALER.**

Inhaler Parts:

See Figures 1 and 2 below to become familiar with the inhaler parts.

Figure 1: Inhaler (upright position)

Figure 2: Inhaler with Cap Removed

Step 1: Open inhaler
Hold the inhaler straight up (upright position) with the colored portion (the base) on the bottom *(see Figure 3 below)*. It is important that you remove the cap of the TWISTHALER while it is in this upright position to make sure that you get the right amount of medicine with each dose.

Holding the colored base, twist the cap in a counterclockwise direction to remove it *(see Figure 3 below)*. As you lift off the cap, the dose counter on the base will count down by one. Removing the cap loads the TWISTHALER with the medicine that you are now ready to inhale.

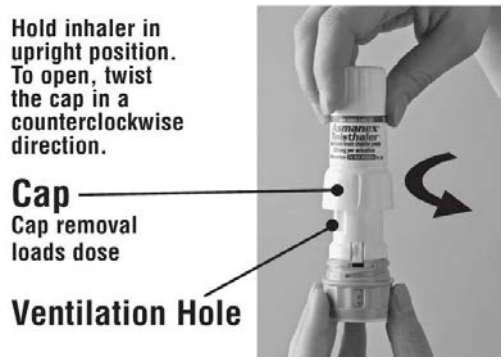


Figure 3: Cap Removal Loads Dose

IT IS IMPORTANT TO NOTE that the indented arrow (located on the white portion of the TWISTHALER, directly above the colored base) is pointing to the dose counter *(see Figure 2)*.

Step 2: Inhale dose
Breathe out fully. Then bring the TWISTHALER up to your mouth or your child's mouth with the mouthpiece facing toward you or your child. Place the mouthpiece in your mouth or your child's mouth, holding it in a horizontal (on its side) position as shown below *(see Figure 4)*. Firmly close your lips around the mouthpiece and take in a fast, deep breath. Since the medicine is a very fine powder, you may not be able to taste, smell, or feel it after inhalation. Do not cover the ventilation holes while inhaling the dose.

Figure 4: Inhalation

Remove the TWISTHALER from your mouth and hold your breath for about 10 seconds, or as long as you comfortably can.

IMPORTANT: DO NOT BREATHE OUT (EXHALE) INTO THE INHALER.

After you take your medicine, it is important that you wipe the mouthpiece dry, if needed, and then **REPLACE THE CAP,** firmly closing the TWISTHALER right away *(see Figures 5 and 6 below)*.

Be sure that the indented arrow is in line with the dose counter. Put the cap back onto the inhaler and turn it in a clockwise direction, as you gently press down. You'll hear a "click" to let you know that the cap is fully closed. This is the only way to be sure that your next dose is loaded the right way.

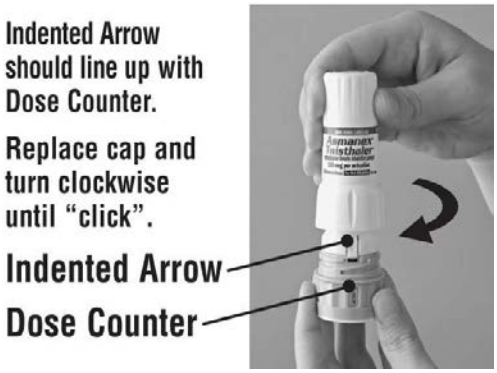


Figure 5: Closing the Inhaler

Figure 6: Closed Inhaler

IT IS IMPORTANT TO REPEAT STEPS 1 AND 2 EACH TIME YOU INHALE.

Rinse your mouth after using.

STORING YOUR INHALER

- Keep your inhaler clean and dry at all times. If the mouthpiece needs cleaning, gently wipe the mouthpiece with a dry cloth or tissue as needed. Do not wash the inhaler. Avoid contact with any liquids.
- **Store in a dry place at 25°C (77°F) [may range between 15-30°C (59-86°F)].**
- Keep your inhaler out of the reach of children.

HOW TO KNOW WHEN YOUR INHALER IS EMPTY
The inhaler has a dose counter on the colored base, which shows the number of doses left to use. As you lift off the cap to take your dose, the dose counter on the base will count down by one (if you began with the dose counter reading "30" this will cause the dose counter to now read "29"). Read the numbers from top to bottom.

When the unit reads "01" this indicates the last remaining dose. After dose "01" the counter will read "00". When you replace the cap, the unit will lock and then must be thrown away. Start using a new ASMANEX TWISTHALER as instructed by your health care provider.

Practical Solutions to Problems Using an Inhaler (10 minutes)

Sticking to a schedule for using an inhaler can be pretty demanding, especially if you take other medications or take them several times a day. If your schedule for medications is very complicated, you may want to discuss with your physician and see if a simpler schedule can be worked out. Sometimes people do all right during the week but have problems keeping on schedule on the weekend or on vacation or traveling because they're not following their regular routine. Handout 14 describes some practical solutions to problems like forgetting your medication, coping with unpleasant side effects, or being embarrassed when you have to use your inhaler in a public place. Let's take a minute to read over the handout and then talk about which of these solutions seems personally useful to each of you. You might also have some suggestions that aren't on the handout.

Practical Solutions to Problems Using an Inhaler

With particular reference to finding specific solutions for class members. Elicit participants' feelings about taking medications on a routine basis.

Overuse of Medications (10 minutes)

Medication *underuse* includes things like*:*

- Skipping doses
- Being careless about the timing of your doses
- Discontinuing routine medications altogether

The opposite side of the coin is medication *overuse.* Surprisingly, the two problems can often go together. When you skip your medications you may be tempted to double up to bring things back under control. *This is much harder on your body* and may even lead to dangerous drug reactions.

In general, there are two dangers associated with medication overuse:

- Overused medication can cause *more side effects* sometimes even severe toxic reactions.

PRACTICAL SOLUTIONS TO PROBLEMS USING AN INHALER

There are several common problems people have trying to stick to their medication plans. Here are some tips and hints for overcoming them.

Problems Solutions

1. Use alarm clocks or watches with built-in alarm functions
2. Take your inhaler at the same time as another regular habit, such as before or after you eat, before you brush your medication teeth, or when you go to bed. Keep them visible.
3. Carry your medicines with you at all times, in your purse, briefcase, etc.; pack in carry-on luggage when traveling.
4. Use a written medication schedule or keep a diary for several weeks until you begin to establish good medication taking habits.
5. Check before a trip to make sure you have enough medication to last until you come back home.

(Affix Label Here) Participant ID: _	Date Form Filled Out: __ __ __ __ __ __ __ __ day month year	Inhaled Mometasone to Promote Reduction of Vaso-occlusive Events

Protocol Orientation Module B

If you lose your medication

Contact study staff immediately:

[redacted]

Pain diaries

Pain diaries are included in your package. Try to fill out a pain diary every day. If you miss a day that's ok. You must fill out at least 30 diaries to stay in the study.

Your medicine

This package contains your medicine for this study. Take one puff of the medicine every day. The research coordinator will teach you how to use the inhaler.

(Affix Label Here) Participant ID: _	Date Form Filled Out: _ _ __ _ _ _ _ __ __ day month year	Inhaled Mometasone to Promote Reduction of Vaso-occlusive Events

Protocol Orientation Module: Adapted from "BREATHE EASIER: AN ADULT ASTHMA EDUCATION PROGRAM" and Mometasone Package Insert

"Breathe Easier"
Developed by the American Institutes for Research and
the Kaiser-Permanente Medical Group
National Heart, Lung, and Blood Institute
National Institutes of Health
National Asthma Education and Prevention Program

(mometasone furoate inhalation)

FOR ORAL INHALATION ONLY

Please read this leaflet carefully before taking your medication.
This leaflet does not contain the complete information about this medication. If you have any questions about this medicine, ask your health care provider or pharmacist.

IMPORTANT POINTS TO REMEMBER

- Use your inhaler regularly and at the same time each day, as prescribed by your health care provider. You or your child may not get the most benefit for 1 to 2 weeks or longer after starting the medication. If you or your child's symptoms do not improve in that time frame or if your condition gets worse, contact your health care provider.
- The inhaler delivers medicine that **you or your child may not taste, smell, or feel**. Do not take or give extra doses unless your health care provider has told you to.
- It is important to replace the cap after each inhalation to protect the inhaler from moisture.
- Do not use the inhaler if you notice that it is not working correctly. Take it to your health care provider or pharmacist.

UNDERSTANDING YOUR MEDICATIONS

MATERIALS FOR SESSION:

• MHWHUHG GRVH LQKDOHUV

As part of this study you will be given an inhaler. This inhaler may contain placebo (no medication) or it may contain a medicine called mometasone. Mometasone is part of a class of medications called corticosteroids.

This is a medication taken regularly every day even when you don't have any symptoms

Although they have a similar name, these steroids are very different from the anabolic steroids that have been in the news in recent years because of their ill-advised use by athletes to increase muscle mass.

Corticosteroids are:

• Anti-inflammatory-Corticosteroids are a very effective anti-inflammatory medication and help reduce or prevent edema and excess mucus in the bronchial tubes.

• Have delayed action-· Corticosteroids do not relax the muscles around the bronchial tubes and will not open the airways immediately as do the bronchodilators. For this reason, they may not *seem* to have any effects. However, over time they can be very beneficial in reducing inflammation.

Inhaled corticosteroids have very few side effects, when used in moderate doses, but they must be taken regularly to be effective.

Possible side effects: an unpleasant taste and gastrointestinal symptoms (e.g., nausea). They may cause a yeast infection ("thrush") in the mouth or bother the upper airways and cause coughing.

Proper Inhaler Use (10 minutes)

The medication that we have been discussing is administered by aerosol inhaler, and proper inhaler use is very important for maximum benefit. If inhalers are not used correctly, the medications don't help much because they can't get all the way down into the narrow airways. Many times patients stop using their inhalers (or, on the other hand, overuse their inhalers) because they think the medicine is not working. In reality, it's not working only because they aren't using it right.

Go over steps while you demonstrate correct usage.

Instruct participants to take one puff per day

Let's take a few minutes to review inhaler use and make sure each of you is using the best technique.

How to Use Your Inhaler

Get Ready

1. Shake the inhaler well for a few seconds before using. Remove the cap.

2. Tilt your head back slightly to straighten the airways to your lungs.

3. Hold the inhaler with your thumb on the bottom and your index or middle finger on top (see picture).

4. Breathe out fully to empty your lungs.

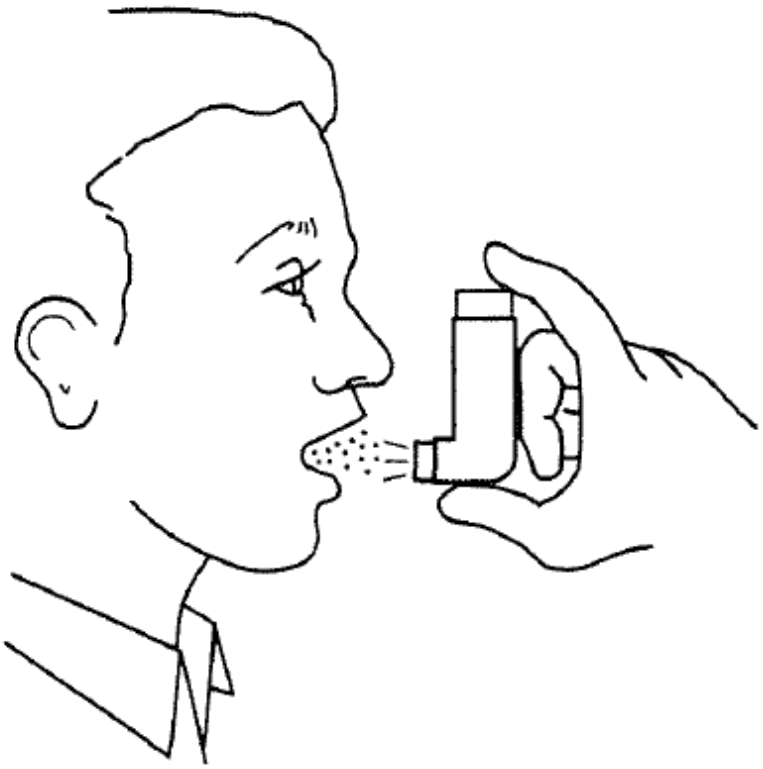
5. Place inhaler 1 to 2 inches in front of your open mouth.*

Inhale Slowly, Press Inhaler

6. Breathe in slowly through your mouth as you press the inhaler once. Keep breathing in slowly without stopping for as long as you can.

Hold Breath

7. Hold your breath for 10 seconds. This allows the medicine to reach deeply into your lungs.



Practical Solutions to Problems Using an Inhaler (10 minutes)

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Supplement 4: Procedures for pulmonary function tests

Exhaled nitric oxide (eNO)

Online F_{ENO} measurement with the NIOX system (Aerocrine AB, Stockholm, Sweden) was performed according to ATS guidelines.[23] F_{ENO} measurement used a resistive device that provided a constant low expiratory flow rate and vellum closure. Participants were required to exhale to residual volume; a mouthpiece was then inserted, and the participant was asked to inhale to total lung capacity. Thereafter, the participant exhaled for 10 seconds at a constant flow rate of 0.05 L/s ± 10%. If a subject did not manage to keep the flow or pressure within the required ranges over the 10 seconds of exhalation, the user profile was changed to 6 seconds per ATS guidelines, and the test was repeated.

Spirometry

After completion of F_{ENO} measurements, spirometry was performed by specially trained and certified research coordinators according to ATS standards,[24] as previously described.[25] Appropriate prediction equations for FEV_1, FVC, and FEV_1/FVC ratio were used, taking into account age, sex, height, and ethnicity.[26] To measure bronchodilator response, technicians administered 2 inhalations of albuterol to participants using an AeroChamber. Spirometry was repeated 15 minutes after albuterol. An increase of 12% or greater in FEV_1 after albuterol was considered a positive bronchodilator response.[27]

Overreading of spirometric and F_{ENO} results

Results were reviewed by a single investigator (G.S.) to ensure ATS criteria were met for spirometry and F_{ENO} measurement; invalid tests were excluded from analyses.

Supplement 5: Attrition

Participant	Reason for attrition	Assignment	Duration of participation
1	Moved out of state	Drug	4 weeks
2	Took one dose and dropped out of study	Placebo	1 week
3	Lost to follow up could not contact	Drug	8 weeks
4	Moved out of the country	Drug	7 weeks
5	Lost to follow up could not contact	Placebo	8 weeks

Supplement 6: Additional Data

Adjusted Intent to treat analyses					
	Placebo (17)	Drug (35)	Treat-ment Effect	95%CI	P value
Additional biological outcomes (pg/mL)					
Δ TNF-α					
Mean (SD)	-0.62 (4.21)	-1.76 (4.38)	-1.00	-3.74 – 1.74	0.47
LS mean (SE)***	-0.66 (1.24)	-1.77 (0.91)			
Median (range)	0.00 (18.37)	-1.08 (20.21)			
Percent change (SD)	-1.78% (8.85)	-1.98% (11.60)			
Δ IFN-γ					
Mean (SD)	-5.59 (13.25)	-5.30 (17.83)	-0.64	-11.04 – 9.76	0.90
LS mean (SE)***	-5.76 (4.71)	-5.45 (3.47)			
Median (range)	-5.37 (52.57)	-1.00 (96.64)			
Percent change (SD)	-1.46% (13.53)	-3.17% (13.67)			
Δ IL1β					
Mean (SD)	-0.96 (4.13)	-0.60 (2.01)	0.05	-1.75 – 1.85	0.96
LS mean (SE)***	-0.98 (0.82)	-0.61 (0.60)			
Median (range)	0.00 (17.45)	-0.24 (9.26)			
Percent change (SD)	4.44% (26.01)	-2.32% (9.53)			
Δ IL-6					
Mean (SD)	-1.94 (5.09)	-1.06 (5.69)	-0.18	-3.52 – 3.16	0.92
LS mean (SE)***	-1.96 (1.51)	-1.08 (1.11)			
Median (range)	-1.00 (22.79)	-0.59 (35.12)			
Percent change (SD)	-5.79% (27.78)	-1.58% (33.11)			
Δ E-selectin					
Mean (SD)	-1899.83 (7241.93)	411.43 (11556.06)	2803.95	-3739.43 – 9347.33	0.86
LS mean (SE)***	-1883.40 (2961.85)	338.75 (2182.35)			
Median (range)	-415.05 (29491.00)	-1711.15 (47937.91)			
Percent change (SD)	-1.40% (19.18)	1.09% (22.65)			
Δ P-selectin					
Mean (SD)	90.26 (7342.84)	209.47 (6622.81)	252.04	-4099.28 – 4603.36	0.91
LS mean (SE)***	-3.14 (1969.62)	173.91 (1451.26)			
Median (range)	292.41 (32713.32)	813.13 (32442.13)			
Percent change (SD)	-2.29% (17.63)	2.49% (19.17)			
Δ IL4					
Mean (SD)	-5.58 (16.92)	-2.20 (17.59)	2.88	-8.13 – 13.88	0.60
LS mean (SE)***	-5.75 (4.98)	-2.21 (3.67)			

Median (range)	-4.83 (61.54)	0.32 (69.31)			
Percent change (SD)	-2.06% (6.30)	0.28% (9.65)			
Δ IL2					
Mean (SD)	12.24 (53.50)	-23.34 (47.38)	-37.39	-79.09 – 4.32	0.08
LS mean (SE)***	12.86 (18.91)	-24.46 (13.62)			
Median (range)	-2.15 (166.69)	-18.69 (183.84)			
Percent change (SD)	8.21% (30.77)	-7.39% (19.66)			
Δ IL13					
Mean (SD)	-272.22 (759.84)	1761.58 (10544.69)	2065.02	-3428.07 – 7558.10	0.45
LS mean (SE)***	-270.46 (2486.48)	1799.18 (1832.06)			
Median (range)	-53.25 (3329.69)	-45.50 (61862.11)			
Percent change (SD)	-4.35% (16.39)	70.73% (418.93)			