

Trial of Roflumilast in Asthma Management (TRIM)

Manual of Procedures Version 1.3

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Revision history

Version 1.3 (11 Dec 2019)

Based on protocol v1.6

MOP Section	v1.2	v1.3
1.1. Design and outcome measures	Methacholine challenge will be performed according to ATS guidelines to assess airway reactivity at visit 2 and at visit 7, only if $FEV_1 \geq 60\%$ predicted.	Methacholine challenge will be performed according to ATS guidelines to assess airway reactivity at visit 2 and at visit 7, only if $FEV_1 \geq 60\%$ predicted and $> 1.5L$.
1.2. Eligibility criteria	Uncontrolled depression as defined by a score of 10 or greater on the depression questions of the PHQ-9	Uncontrolled depression as defined by a score of 15 or greater on the depression questions of the PHQ-9
1.3. Study visit time window and data collection schedule	Methacholine for those with $FEV_1 \geq 60\%$ predicted, all others simple spirometry (without bronchodilator)	Methacholine for those with $FEV_1 \geq 60\%$ predicted and $> 1.5L$, all others simple spirometry (without bronchodilator)
2.1. Screening (V1)	If the total PHQ-9 score (item 10) or the total GAD-7 score (item 19) is 10 or more, participant is ineligible for study, and should be given mental health resource information.	If the total PHQ-9 score (item 10) is 15 or more or the total GAD-7 score (item 19) is 10 or more, participant is ineligible for study, and should be given mental health resource information.
2.2. Follow-up visit (V2)	- Methacholine challenge test supplies, if $FEV_1 \geq 60\%$ predicted (If $FEV_1 < 60\%$ predicted), perform spirometry) - Spirometry supplies, if $FEV_1 < 60\%$ predicted - If the total PHQ-9 score (item 10) or the total GAD-7 score (item 19) is 10 or more, participant is ineligible for study, and should be given mental health resource information. - If participant's $FEV_1 < 60\%$ predicted, spirometry should be performed instead of the methacholine challenge test	- Methacholine challenge test supplies, if $FEV_1 \geq 60\%$ predicted and $> 1.5L$ (If $FEV_1 < 60\%$ predicted and $< 1.5L$), perform spirometry) - Spirometry supplies, if $FEV_1 < 60\%$ predicted and $< 1.5L$ - If the total PHQ-9 score (item 10) is 15 or more or the total GAD-7 score (item 19) is 10 or more, participant is ineligible for study, and should be given mental health resource information. - If participant's $FEV_1 < 60\%$ predicted and $< 1.5L$, spirometry should be performed instead of the methacholine challenge test
2.3. Follow-up visit (V3) 2.4. Follow-up visit (V4) 2.5. Follow-up visit (V5) 2.6. Follow-up visit (V6)	If the total PHQ-9 score (item 10) or the total GAD-7 score (item 19) is 10 or more, participant is ineligible for study, and should be given mental health resource information.	If the total PHQ-9 score (item 10) is 15 or more or the total GAD-7 score (item 19) is 10 or more, or if there is a change in score totaling 5 or more, from baseline (V2), participant should be given mental health resource information.

2.7. End of treatment visit (V7)	• Methacholine challenge test supplies, if FEV₁ ≥ 60% predicted • Spirometry supplies if FEV₁ < 60% predicted • If the total PHQ-9 score (item 10) or the total GAD-7 score (item 19) is 10 or more, participant is ineligible for study, and should be given mental health resource information. • If participant's FEV₁ < 60% predicted, spirometry should be performed instead of the methacholine challenge test	• Methacholine challenge test supplies, if FEV₁ ≥ 60% predicted and > 1.5L • Spirometry supplies if FEV₁ < 60% predicted and < 1.5L • If the total PHQ-9 score (item 10) is 15 or more or the total GAD-7 score (item 19) is 10 or more, or if there is a change in score totaling 5 or more, from baseline (V2), participant should be given mental health resource information. • If participant's FEV₁ < 60% predicted and < 1.5L, spirometry should be performed instead of the methacholine challenge test
5.2. Blood draws	• 200-300 mg/dL • 300+ mg/dL	• 200-299 mg/dL • ≥300 mg/dL
5.5.4. Patient Health Questionnaire (PHQ-9 and GAD-7)	• At V1 and V2: If the total PHQ-9 score (item 10) and the total GAD-7 score (item 19) is 10 or more points, participant should not be enrolled or randomized • At V3-V7: If the total PHQ-9 score (item 10) and the total GAD-7 score (item 19) is 10 or more points	• At V1 and V2: If the total PHQ-9 score (item 10) is 15 or more and the total GAD-7 score (item 19) is 10 or more points, participant should not be enrolled or randomized • At V3-V7: If the total PHQ-9 score (item 10) is 15 or more and the total GAD-7 score (item 19) is 10 or more points OR
5.5.5. Handling elevated symptoms: Depression, anxiety, and self-harm	• Elevated depression scores are defined as: Total score of 10 or greater on the depression questions of the PHQ-9 (HQ form).	• Elevated depression scores are defined as: Total score of 15 or greater on the depression questions of the PHQ-9 (HQ form).

Version 1.2 (11 Jul 2019)
Based on protocol v1.5

MOP Section	V1.1	v1.2
1.1. Design and outcome measures	• Fasting blood will be stored for measurement of markers of metabolic dysfunction.	• Blood specimens will be collected for fasting blood glucose and analysis of metabolic and oxidative markers related to asthma. Excess blood specimens will be used for future asthma research with the patient's consent. Fasting blood draw may take place within 7 days of rest of the procedures scheduled for visit 2 or visit 7.
1.2. Eligibility criteria		• Added generalized anxiety disorder to major psychiatric disorder exclusion criteria

1.3. Study visit time windows and data collection schedule	Fasting blood glucose	- Blood collection* *Collection for fasting blood glucose and metabolic and oxidative markers. Excess blood specimens will be used for future research, if participant consents.
3.1.4. Receipt and drug distribution	Incorrect email address (JHPSH. Ala-acrc@jhu.edu)	Correct email address (JHSPH.ala-acrc@jhu.edu)
4.3.1. General certification requirements	N/A	- Psychologist/licensed psychologist- used as a resource for the PI if a participant presents with elevated depression, anxiety, or suicidal thoughts - The assigned psychiatrist/licensed psychologist should take the general knowledge assessment. Please email the DCC if you have any issues.
4.4.2. Study supplies	2 mL orange top aliquot tubes	10 mL tiger top aliquot tubes
5.4. Specimen collection	Biospecimens (serum) will be collected for future studies (optional)	Biospecimens (serum) will be collected for metabolic and oxidative markers (not optional) and future studies (optional)
5.5.5. Handling elevated symptoms: Depression, anxiety, and self-harm		- Added "identify a psychologist or licensed psychologist to be used a resource for your site" - Added follow-up information for participants with elevated depression/anxiety scores Note: If the participant has elevated scores, refer them to get further evaluation and treatment, document the referral to the patient and their primary care physician/mental health provider, and document the event as an unanticipated problem on a UP form.
Appendix H, I		H. Recruitment scripts I. Schedule of Visits

Version 1.0 (19 Jul 2018)
Based on protocol v1.0

Version 1.1 (28 Nov 2018)
Based on protocol v1.3

MOP Section	V1.0	v1.1
1.3. Design and outcome measures	Methacholine challenge will be performed according to ATS guidelines to assess airway reactivity at visit 2 and at visit 7, only if FEV₁ ≥ 60% predicted.	- Methacholine challenge will be performed according to ATS guidelines to assess airway reactivity at visit 2 and at visit 7, only if FEV₁ ≥ 60% predicted. Participants with no current or previous methacholine within the past 5 years can use the methacholine test at V2 as a screener to determine eligibility. - Clarification of drug titration

1.2. Eligibility criteria	- Inclusion: - Current or previous (within two years) evidence of at least a 12% increase in FEV₁ after inhaling 2-4 puffs of albuterol or a positive methacholine challenge (a $\geq$ 20% decrease in FEV₁ when compared to baseline) - Exclusion: - Illegal drug use in the past year - Cannabis use in the past year	- Inclusion: - Current or previous (within five years) evidence of at least a 12% increase in FEV₁ after inhaling 2-4 puffs of albuterol or a positive methacholine challenge (a $\geq$ 20% decrease in FEV₁ when compared to baseline) - Exclusion: > 0 illegal drug use in the past year > 0 cannabis use in the past year
2.0 Study visits/contacts	Pre-bronchodilator spirometry efforts should be performed when it has been at least 4 hours since participant's last dose of short-acting bronchodilator	Removed this sentence. Proceed with spirometry just note if they took pre and/or post bronchodilator
2.1-2.7 Study visit procedures	Tape measure	- Extended tape measure - Addition of the instructions below at each visit - If the total PHQ-9 score (item 10) or the total GAD-7 score (item 19) is 10 or more, participant is ineligible for study, and should be given mental health resource information. - Updated Drug Return/Tablet count tasks at each visit - Updated Distribute and review at each visit - Updated 2.7 procedures
3.0. Treatment administration		Addition of study dosing schedules and rearranging of contents
3.1.4. Receipt and drug distribution	At room temperature, (59-86°F)	At room temperature (68-77°F); excursions permitted to (59-86°F).
5.1.1. Spirometry procedures		Addition of the following information: - Note: <i>Proceed with spirometry testing even if participant indicates they have taken short or long acting bronchodilator prior to the clinic visit. Make sure to indicate whether they have taken either medication on the Pulmonary Function (PF) form (item 8).</i> - The EasyOn spirometer needs to be calibrated by doing a single flow check before each test and a multi-flow check once a week.
Appendix E, F, G		- Addition of Appendices: E. Drug information sheet F. Fasting blood sugar sample letter G. Unmasking letter

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1. Study overview

1.1 Design and outcome measures

Title

Trial of Roflumilast in Asthma Management (TRIM)

Objectives

The purpose of this protocol is to pilot test roflumilast for the treatment of poorly controlled obese asthmatics to determine the effectiveness and tolerability of the intervention.

1. The primary outcome of this study is to see a change in asthma control at 24 weeks measured by the Asthma Control Test in participants assigned to roflumilast or placebo.
2. The secondary outcomes include: spirometry, airway reactivity, asthma quality of life, episodes of poor asthma control from diary cards, BMI, and gastrointestinal symptoms.

Type of study

- Randomized, two parallel arm, placebo-controlled clinical trial
- Multicenter, 5 clinical centers
- Fixed sample size; 38
- Allocation ratio 1:1

Study treatment

- Roflumilast OR
- Placebo

Drug titration

Day 1 (randomization at V2) to V3 (2 weeks)

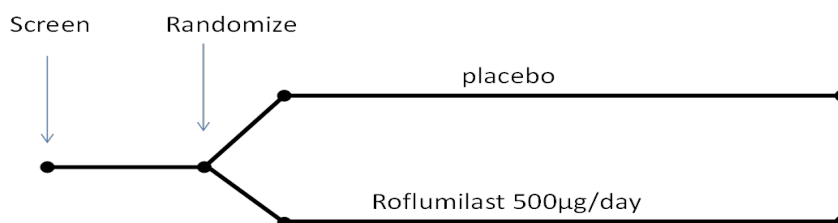
Roflumilast 500 µg every other day (one tablet) OR placebo (one tablet)

Day 15 at V3 to V7 (22 weeks)

If well tolerated: roflumilast 500 µg per day (one tablet) OR placebo (one tablet)

Study design

1 week baseline ← 24 week treatment →



V1	V2	V3	V4	V5	V6	V7
wk-1	wk0	wk2	wk6	wk12	wk18	wk24

Assessments

- Asthma diaries completed by participants to record daily morning peak expiratory flow (PEF), daily asthma symptom scores, beta-agonist use for symptoms, nocturnal asthma awakenings, and health care use. Diary data are used to identify episodes of poor asthma control and days with no asthma symptoms (asthma-free days).
- Asthma Control Test (ACT) is a questionnaire with 4-week recall period measures asthma control.
- Marks Asthma Quality of Life Questionnaire (Marks AQLQ) assesses asthma specific quality of life.
- Asthma Symptom Utility Index (ASUI) is a 2-week utility-weighted asthma symptom questionnaire.
- Gastrointestinal Symptom Rating Scale (GSRS) assess GI side effects. It is a 15-item instrument with five subscales (reflux, diarrhea, constipation, abdominal pain and indigestion). The five subscales of the questionnaire produce a mean score ranging from 1 (no discomfort) to 7 (very severe discomfort).
- Patient Health Questionnaire (PHQ) is a diagnostic tool for mental health disorders. We use sections specific to depression (PHQ-9) and anxiety (GAD-7). This form asks a series of questions on whether or not a participant has been bothered by problems with depression, anxiety, or suicidal thoughts over the last 2 weeks.
- Suicide Severity Screener (SSW) has been adapted from the Columbia-Suicide Severity Rating Scale (C-SSRS). This form will only be used when a participant discloses that they may do harm to themselves as indicated by a score of greater than 0 on Question 9 on the PHQ-9.
- Anthropometrics, height and weight, and waist and hip circumference per NHANES III.
- Spirometry per ATS/ERS standards.²⁸ Patients will undergo spirometry with bronchodilator testing at V1, all others will be spirometry without bronchodilator.
- Methacholine challenge will be performed according to ATS guidelines to assess airway reactivity at visit 2 and at visit 7, only if $FEV_1 \geq 60\%$ predicted and $> 1.5L$. Participants with no current or previous methacholine within the past 5 years can use the methacholine test at V2 as a screener to determine eligibility.
- Adverse effects will be assessed by open-ended questions at each visit and rated in severity.
- Interval health history will be recorded at each clinic visit. Records of all hospitalizations and, if necessary, deaths are obtained for verification of diagnoses and assessment of safety issues.
- Baseline questionnaires and exam will be administered to ascertain demographics including self-reported ethnicity and race, general health, co-morbid conditions, asthma symptoms, and medication use.
- Assessment of Adherence: adherence will be assessed from pill counts at each study visit after randomization.
- Exit questionnaires will be administered at the last visit to determine global assessments of treatment, satisfaction with study procedures and personnel, and opinions about the intervention.
- Blood specimens will be collected for fasting blood glucose and analysis of metabolic and oxidative markers related to asthma. Excess blood specimens will be used for future asthma research with the patient's consent. Fasting blood draw may take place within 7 days of rest of the procedures scheduled for visit 2 or visit 7.

1.2 Eligibility criteria

Inclusion criteria

- Physician diagnosis of asthma on regular prescribed controller therapy for at least 3 months
- Current or previous (within five years) evidence of at least a 12% increase in FEV₁ after inhaling 2-4 puffs of albuterol or a positive methacholine challenge (a $\geq$ 20% decrease in FEV₁ when compared to baseline)
- Age: $\geq$ 18 years of age
- Obese: BMI $>$ 30 kg/m²
- Poorly controlled asthma:
 - Asthma Control Test (ACT) Score $<$ 20, or
 - use of rescue inhaler on average of $>$ 2 uses/week for preceding month, or
 - nocturnal asthma awakening on average of 1 or more times/week in preceding month, or
 - ED/hospital visit or prednisone course for asthma in past six months.
- Ability and willingness to provide informed consent

Exclusion criteria

- Participation in a study of an investigational agent or intervention within the past 4 weeks
- Physician diagnosis of chronic obstructive pulmonary disease (COPD)
- Any condition that puts the participant at risk from weight loss as judged by the site physician
- Liver cirrhosis
- Major psychiatric disorders such as generalized anxiety disorder, major depressive disorder, history of suicidal ideation/ attempt, panic disorder, post-traumatic stress disorder, schizophrenia, schizoaffective disorder, substance abuse or other disorders that in the opinion of the study physician that would affect study participation
- Uncontrolled depression as defined by a score of 15 or greater on the depression questions of the PHQ-9
- Suicidal ideation (a score of greater than 0 on Question 9 on the PHQ-9)
- Uncontrolled anxiety defined by a score of 10 or greater on the anxiety questions of the GAD-7
- $>$ 0 times of illegal drug use in the past year
- $>$ 0 times of cannabis use in the past year
- Pregnancy/lactation
- Females of childbearing age who do not agree to practice an adequate birth control method (abstinence, combination barrier and spermicide, or hormonal) for the duration of the study.
- Greater than 20 pack year smoking history, or smoking within the last 6 months.
- History of bariatric surgery
- Current use of drugs metabolized by cytochrome P450 (rifampicin, phenobarbital, carbamazepine, phenytoin, erythromycin, ketoconazole, cimetidine, fluvoxamine, enoxacin, oral contraceptives containing ethinyl estradiol with gestodene).
Please note: Oral contraceptives containing ethinyl estradiol with gestodene drugs are not available in the United States; please refer to the following link for drug list:
<https://www.drugs.com/international/gestodene.html>
- Currently on roflumilast or theophylline (patient may wash out of these medications for 4 weeks prior to visit 1).

1.3. Study visit time windows and data collection schedule

Outline of Study Visits							
Week	-1	0	2	6	12	18	24
Visit number	V1	V2	V3	V4	V5	V6	V7
Consent	•						
Baseline/interim history	•	•	•	•	•	•	•
Collect diary cards		•	•	•	•	•	•
Pill Counts			•	•	•	•	•
Spirometry	•‡		•	•	•	•	
Methacholine¥		•¥					•¥
Asthma Control	•	•	•	•	•	•	•
Anxiety/depression questionnaires	•	•	•	•	•	•	•
GSRS	•	•	•	•	•	•	•
QOL	•	•	•	•	•	•	•
Anthropometrics	•	•	•	•	•	•	•
Blood draw (fasting)*		•					•
Pregnancy test §	•	•	•	•	•	•	•
End of study questionnaire							•

Key: § for women of child-bearing potential

‡ Spirometry at visit 1 only will be pre and post bronchodilator, all other visits spirometry without bronchodilator

¥ Methacholine for those with $FEV_1 \geq 60\%$ predicted and $> 1.5L$, all others simple spirometry (without bronchodilator)

*Collection for fasting blood glucose and metabolic and oxidative markers for asthma. Excess blood specimens will be used for future research, if participant consents.

2. Study visits/contacts

Overall study visits

There is no specified order for study visit procedures. However, it is recommended that the quality of life and asthma control questionnaires be completed at the beginning of the visit so that the responses are not influenced by study visit procedures. Please administer more sensitive questionnaires such as PHQ-9 and GAD-7 at the end of the visit.

Questionnaires

- Asthma Control Test (ACT)
- Asthma Symptom Utility Index (ASUI)
- Marks Asthma Quality of Life Questionnaire (Marks AQLQ)
- SF-36™ Version 1.0 (SF-36)
- Gastrointestinal Symptom Rating Scale (GSRS)
- The Patient Health Questionnaire for Depression and Anxiety (PHQ-9 and GAD-7)
- Suicide Severity Screener (SSW)

Lung function procedures

All participants are to have pre- and post-bronchodilator spirometry testing at V1, and spirometry without bronchodilator at V3, V4, V5, and V6.

- Proceed with spirometry testing even if participant indicates they have taken short or long acting bronchodilator prior to the clinic visit. Make sure to indicate whether they have taken either medication on the Pulmonary Function (PF) form (item 8).

Trial schema terminology

Pre-screening

- Participant information is entered into the Participant Screening log (PS)
- Participant may not have signed consent

Registration

- A participant is registered when the participant ID is assigned

Enrollment

- Participant signs consent
- Evaluated for eligibility
- When participant completes V1, they are “enrolled”

Intervention

- Participant is randomized to roflumilast or placebo at V2
- All randomized participants are included in the primary analysis

2.1. Screening (V1)

Overview

V1 includes the consenting process, initial screening for eligibility, questionnaires, spirometry (with pre and post bronchodilator), health history, pregnancy test (if applicable), blood pressure, and anthropometrics (height, weight, BMI, waist-hip ratio). Subjects eligible for enrollment will be given TRIM Diary (DC) Cards to be filled out daily and returned at V2.

Time frame

- Target- 1 week prior to randomization (V2)
- Window- 0 to 2 weeks before randomization (V2)
- Duration- 1 to 2 hours

Equipment/materials

- Consent form
- Participant binder
- Spirometer
- Mini-Wright Peak Flow Meters
- Albuterol
- General asthma education materials (Asthma Action Plan)
- TRIM Diary (DC) Cards
- Pregnancy test (for female participants of childbearing potential)
- Extended tape measure
- Automated blood pressure cuff
- Participant Instruction Sheets
 - Methacholine Challenge Test
 - Asthma Diary Cards
 - Measuring Peak Flow
- V1 forms and V1 checklist

Tasks

- Explain study to participant
- Review consent with participant
- Sign and date consent form and provide copy to participant
- Assign participant ID using the next sequentially numbered label on Clinic Label Sheet (see example in Section 7.2.1)
 - Register participant number in TRIM data system
 - Place label in box on item 2 of Screening (SC) form
- Pregnancy test (for female participants of childbearing potential)
 - If test is positive STOP, participant is not eligible
- Complete Participant Information Sheet (PI)
- Check height, weight, and waist and hip circumference (PM)
- Blood pressure measurement (PM)

- Questionnaires
 - Coordinator administers: Asthma Symptom Utility Index (AS)
 - Have participant complete:
 - Asthma Control Test (TA)
 - Marks Quality of Life Questionnaire (MQ)
 - Quality of Life Questionnaire (SF)
 - Gastrointestinal Symptom Rating Scale (GS)
 - Patient Health Questionnaire for Depression and Anxiety (HQ)
- Administer the Suicidality Severity Screener (SSW) form if participant scores greater than a 0 on item 9 of the Patient Health Questionnaire for Depression and Anxiety (HQ)
 - If the total PHQ-9 score (item 10) is 15 or more or the total GAD-7 score (item 19) is 10 or more, participant is ineligible for study, and should be given mental health resource information.
- Complete forms and procedures:
 - Screening (SC) form
 - Baseline Asthma and Medical History (BA) form
 - Physical Exam (PE), if participant who have not been seen in the study physician's clinic within the last 12 months
- Pulmonary function testing (PF) form- collect pre- and post- bronchodilator PFT data; printout of spirometry session to be stored as source documentation
- Complete Medications Log (non-asthma/non-allergy) (CM)
- Complete Asthma and Allergy Medications Log (AA)
- Distribute and review
 - TRIM Schedule of Visits (SOV) with dates and times for all subsequent visits recorded, if possible
 - Participant binder
 - Peak Flow Meter and Instructions for Measuring Peak Flow (IPF)
 - Provide instruction, both verbal and written, on how to use
 - Have participant perform 3 peak flows, record the highest of three efforts
 - Instruct participant to bring peak flow meter to all visits
 - Fill out, and provide participant with Asthma Action Plan Card (AAP)
 - Fill in personal best peak flow from the highest of three efforts, and calculate zone cut-offs. Record zone cut-offs on the card and give to participant
 - Review instructions for TRIM Diary (DC) Cards with the participant
 - Give them enough diary cards to fill out each day until the next clinic visit
 - Provide and review the Instructions for TRIM Diary Cards (IDC) with participant
 - Provide and review the Instructions for Methacholine Challenge Test with participant
- Schedule participant to come back for Visit 2 (V2), ideally one week after V1
- After visit
 - Send Primary Physician "Introduction letter to primary asthma physician" (sample letter in section 8.1)
 - Include a copy of spirometry results

- Data enter:
 - Update participant screening log if participant is ineligible
 - Key SC form into the data system **within 5 working days**, if the participant is eligible, and before participant comes in for V2
 - Enter remaining forms and questionnaires into TRIM data system within 10 working days

Forms (abbreviation)

- Screening form (SC)
- Baseline Asthma and Medical History (BA)
- Participant Information (PI)*
- Pulmonary Function Testing (PF)
- TRIM Diary (DC) Cards
- Physical Measurements (PM)
- Physical Exam (PE), if necessary
- Suicide Severity Screener (SSW)*, if needed

Questionnaires (abbreviation)

- Asthma Symptom Utility Index (AS) (coordinator completes)
- Asthma Control Test (TA)
- Marks Quality of life questionnaire (MQ)
- Quality of Life Questionnaire (SF)
- Gastrointestinal Symptom Rating Scale (GS)
- Patient Health Questionnaire for Depression and Anxiety (HQ)

Log/Administrative forms (abbreviation)

- Unanticipated Problem (UP) or Serious Adverse Event (SR), if needed
- Participant Screening Log (PS)
- Medications Log (non-asthma/non-allergy) (CM) (entered into database after final study visit)
- Asthma and Allergy Medications Log (AA) (entered into database after final study visit)

Instruction sheets (abbreviation)

- Instructions for Measuring Peak Flow (IPF)
- Instructions for TRIM Diary Cards (IDC)
- Instructions for Methacholine Challenge Test (IMC)

*Not data entered

2.2. Follow up visit (V2)

Overview

The primary purpose of V2 is randomization, i.e., treatment assignment. V2 includes confirmation of eligibility, questionnaires, assessment of adverse events, methacholine challenge test, interim health history, pregnancy test (if applicable), blood pressure, anthropometrics, and a blood draw (this may be completed on a separate day, within 1 week of the actual V2 visit). For randomized participants, the visit includes distribution of study drug. Participants will be given TRIM Diary (DC) Cards to be filled out daily and returned at V3.

Time frame

- Target- 1 week after screening visit (V1)
- Window- 1 to 2 weeks after V1
- Duration- 2 to 2 ½ hours

Equipment/materials

- V2 forms and V2 checklist
- Methacholine challenge test supplies, if $FEV_1 \geq 60\%$ predicted and $> 1.5L$ (If $FEV_1 < 60\%$ predicted and $< 1.5L$), perform spirometry)
 - AeroEclipse II
 - Breath actuated nebulizer
 - Rotameter/precision flow meter
 - EasyOn spirometer
 - Laptop
- Spirometry supplies, if $FEV_1 < 60\%$ predicted and $< 1.5L$
 - Mini-Wright Peak Flow Meters
 - Albuterol (MDI or nebulizer depending on clinic's standard protocol)
- Specimen collection, processing and storage supplies
- Pregnancy test (for females of childbearing potential)
- Extended tape measure
- Automated blood pressure cuff
- Information Sheet about Study Drug

Tasks

- One-day prior, call participant to remind them about fasting blood draw and medication holds for the methacholine challenge test
- Pregnancy test (for female participants of childbearing potential)
 - If test is positive STOP, participant is not eligible
- Check weight, and waist and hip circumference (PM)
- Blood pressure measurement (PM)
- Questionnaires
 - Coordinator completes Asthma Symptom Utility Index (AS) with participant's input
 - Have participant complete:
 - Asthma Control Test (TA)
 - Marks Quality of Life Questionnaire (MQ)
 - Quality of Life Questionnaire (SF)
 - Gastrointestinal Symptom Rating Scale (GS)
 - Patient Health Questionnaire for Depression and Anxiety (HQ)

- Administer the Suicidality Severity Screener (SSW) form if participant scores greater than 0 on item 9 of the Patient Health Questionnaire for Depression and Anxiety (HQ)
 - If the total PHQ-9 score (item 10) is 15 or more or the total GAD-7 score (item 19) is 10 or more, participant is ineligible for study, and should be given mental health resource information.
- Complete forms and procedures:
 - Clinic Visit (CV) Form, includes interim medical history
 - Medications Log (non-asthma/non-allergy) (CM)
 - Asthma and Allergy Medications Log (AA)
- Methacholine testing (See separate Methacholine MOP)
 - If participant's FEV₁ < 60% predicted and < 1.5L, spirometry should be performed instead of the methacholine challenge test
- Review TRIM Diary (DC) Cards with participant and guide participant to make edits if any are required
- Fasting blood draw: patient should fast from midnight and blood should be collected prior to 11 am. Participant may eat and drink after blood is collected.
- Screen for adverse events.
- Review instructions for use of Asthma Action Plan Card (AAP).
- If participant is not eligible to proceed into the study, update the Participant Screening Log (PS).
 - Complete Early Study Exit (EE) form and data enter within 10 working days
 - A participant that is not eligible at V2 to be randomized may be eligible to be rescreened (See MOP section 2.9). Eligibility must occur within 14 days of V1.
- If participant meets all eligibility criteria, then he/she may be enrolled into the study
 - If eligible, data enter EL form
- Perform treatment assignment by completing the "TRIM Treatment Assignment (Randomization)" on the main data system page. This step must be completed before giving any drug to the participant.
- Complete Drug Dispensing (DA) form:
 - Make sure you distribute the correct bottle assigned by the data system
 - Affix the tear-off label from drug package onto the DA form **at the time drug is assigned to the participant**
 - **Key DA form into data system while participant is at the clinic** to avoid errors in drug distribution.
- Distribute and review
 - TRIM Diary (DC) Cards to be brought back at V3
 - ACRC appointment card for V3
 - Provide and review the Information Sheet about Study Drugs with participant (See letter in Appendix E)
 - Dispense study drug bottle to participant after filling in label on bottle with:
 - Bottle ID:
 - Date Dispensed
 - Physician
 - Emergency study contact #
 - Patient Name
 - Expiration date
 - Study drug directions for use

*Note: use a ballpoint pen when writing on the bottle label.

- Instruct participant:
 - Study drug should be taken according to the following dosing schedule:
 - Randomization at visit 2- 1 tablet every other day
 - Visit 3 onward (2 weeks after V2)- 1 tablet every day, if tolerated
 - Missed doses are not “made up” (do not double the next dose)
 - Study drug can be taken with food to prevent stomach upset
- After visit
 - Enter remaining forms and questionnaires into TRIM data system within 10 working days.
 - If participant is randomized, send physician introduction letter (see prototype in MOP section 8.1) to participant’s primary pulmonary physician

Forms (abbreviation)

- Clinic Visit (CV)
- Drug Dispensing (DA)
- Biospecimen Collection (BC)
- Methacholine form (MC)
- Pulmonary Function Testing (PF), if needed
- TRIM Diary (DC) Cards
- Physical Measurements (PM)
- Eligibility Form (EL)
- Suicide Severity Screener (SSW)*, if needed

Questionnaires (abbreviation)

- Asthma Symptom Utility Index (AS) (coordinator completes)
- Asthma Control Test (TA)
- Marks Quality of life questionnaire (MQ)
- Quality of Life Questionnaire (SF)
- Gastrointestinal Symptom Rating Scale (GS)
- Patient Health Questionnaire for Depression and Anxiety (HQ)

Log/Administrative forms (abbreviation)

- Unanticipated Problem (UP) or Serious Adverse Event (SR), if needed
- Participant Screening Log (PS), if needed
- Early Study Exit (EE), if needed
- Medications Log (non-asthma/non-allergy) (CM) (entered into database after final study visit)
- Asthma and Allergy Medications Log (AA) (entered into database after final study visit)

Instruction sheet

- Information Sheet about Study Drugs

* Not data entered

2.3. Follow up visit (V3)

Overview

V3 includes questionnaires, assessment of adverse events, spirometry, interim health history, pregnancy test (if applicable), blood pressure, anthropometrics, and pill counts. Participants will be given TRIM Diary (DC) Cards to be filled out daily and returned at V4.

Time frame

- Target- 2 weeks after randomization (V2)
- Window- 2 to 3 weeks after V2
- Duration- 1 to 1 ½ hours

Equipment/materials

- V3 forms and V3 checklist
- Spirometer
- Pregnancy test (for females of childbearing potential)
- Extended tape measure
- Automated blood pressure cuff

Tasks

- Pregnancy test (for female participants of childbearing potential)
 - If test is positive STOP, participant is no longer eligible, fill out a Treatment Termination (TT) form and instruct participant to return study drug
- Check weight, and waist and hip circumference (PM)
- Blood pressure measurement (PM)
- Drug Return/Tablet Count
 - Complete Drug Return/Tablet Count (DR) form
 - Count tablets and record on form. Tablets should be counted at least twice, or until results can be repeated (**Count tablets using gloves and pill counter in front of participant**)
 - Determine approximate expected number of remaining tablets and compare to actual number returned
- Questionnaires
 - Coordinator completes Asthma Symptom Utility Index (AS) with participant's input
 - Have participant complete:
 - Asthma Control Test (TA)
 - Marks Quality of Life Questionnaire (MQ)
 - Quality of Life Questionnaire (SF)
 - Gastrointestinal Symptom Rating Scale (GS)
 - Patient Health Questionnaire for Depression and Anxiety (HQ)
- Administer the Suicidality Severity Screener (SSW) form if participant scores greater than 0 on item 9 of the Patient Health Questionnaire for Depression and Anxiety (HQ)
 - If the total PHQ-9 score (item 10) is 15 or more or the total GAD-7 score (item 19) is 10 or more, or if there is a change in score totaling 5 or more, from baseline (V2), participant should be given mental health resource information.

- Complete forms and procedures:
 - Clinic Visit (CV) Form, includes interim medical history and study drug dose and tolerability
 - Medications Log (non-asthma/non-allergy) (CM)
 - Asthma and Allergy Medications Log (AA)
- Pulmonary function testing (PF) form- collect pre- bronchodilator PFT data; results are recorded on the pulmonary Function Form (PF). Printout of spirometry session to be stored as source documentation
- Review TRIM Diary (DC) Cards with participant and guide participant to make edits if any are required
- Screen for adverse events.
- Distribute and review
 - TRIM Diary (DC) Cards to be brought back at V4
 - ACRC appointment card for V4
 - If needed; dispense study drug bottle to participant after filling in label on bottle with:
(No follow up bottle dispensed at this visit based on protocol)
 - Bottle ID:
 - Date Dispensed
 - Physician
 - Emergency study contact #
 - Patient Name
 - Expiration date
 - Study drug directions for use
- *Note: use a ballpoint pen when writing on the bottle label.
- After visit
 - Enter remaining forms and questionnaires into TRIM data system within 10 working days.

Forms (abbreviation)

- Clinic Visit (CV)
- Drug Dispensing (DA), if needed
- Drug Return/Tablet Count (DR)
- Pulmonary Function Testing (PF)
- TRIM Diary (DC) Cards
- Physical Measurements (PM)
- Suicide Severity Screener (SSW)*, if needed
- Treatment Termination (TT), if needed

Questionnaires (abbreviation)

- Asthma Symptom Utility Index (AS) (coordinator completes)
- Asthma Control Test (TA)
- Marks Quality of life questionnaire (MQ)
- Quality of Life Questionnaire (SF)
- Gastrointestinal Symptom Rating Scale (GS)
- Patient Health Questionnaire for Depression and Anxiety (HQ)

Log/Administrative forms (abbreviation)

- Unanticipated Problem (UP) or Serious Adverse Event (SR), if needed
- Early Study Exit (EE), if needed
- Medications Log (non-asthma/non-allergy) (CM) (entered into database after final study visit)
- Asthma and Allergy Medications Log (AA) (entered into database after final study visit)

* Not data entered

2.4. Follow up visit (V4)

Overview

V4 includes questionnaires, assessment of adverse events, spirometry, interim health history, pregnancy test (if applicable), blood pressure, anthropometrics, and pill counts. Participants will be given TRIM Diary (DC) Cards to be filled out daily and returned at V5.

Time frame

- Target- 6 weeks after randomization (V2)
- Window- 5 to 7 weeks after V2
- Duration- 1 to 1 ½ hours

Equipment/materials

- V4 forms and V4 checklist
- Spirometer
- Pregnancy test (for females of childbearing potential)
- Extended tape measure
- Automated blood pressure cuff

Tasks

- Pregnancy test (for female participants of childbearing potential)
 - If test is positive STOP, participant is no longer eligible, fill out a Treatment Termination (TT) form and instruct participant to return study drug
- Check weight, and waist and hip circumference (PM)
- Blood pressure measurement (PM)
- Drug Return/Tablet Count
 - Complete Drug Return/Tablet Count (DR) form
 - Count tablets and record on form. Tablets should be counted at least twice, or until results can be repeated (Count tablets using gloves and pill counter in front of participant)
 - Determine approximate expected number of remaining tablets and compare to actual number returned
- Questionnaires
 - Coordinator completes Asthma Symptom Utility Index (AS) with participant's input
 - Have participant complete:
 - Asthma Control Test (TA)
 - Marks Quality of Life Questionnaire (MQ)
 - Quality of Life Questionnaire (SF)
 - Gastrointestinal Symptom Rating Scale (GS)
 - Patient Health Questionnaire for Depression and Anxiety (HQ)
- Administer the Suicidality Severity Screener (SSW) form if participant scores greater than 0 on item 9 of the Patient Health Questionnaire for Depression and Anxiety (HQ)
 - If the total PHQ-9 score (item 10) is 15 or more or the total GAD-7 score (item 19) is 10 or more, or if there is a change in score totaling 5 or more, from baseline (V2), participant should be given mental health resource information.

- Complete forms and procedures:
 - Clinic Visit (CV) Form, includes interim medical history and study drug dose and tolerability
 - Medications Log (non-asthma/non-allergy) (CM)
 - Asthma and Allergy Medications Log (AA)
 - Pulmonary function testing (PF) form- collect pre- bronchodilator PFT data; results are recorded on the pulmonary Function Form (PF). Printout of spirometry session to be stored as source documentation
 - Review TRIM Diary (DC) Cards with participant and guide participant to make edits if any are required
 - Screen for adverse events.
 - Distribute and review
 - TRIM Diary (DC) Cards to be brought back at V5
 - ACRC appointment card for V5
 - Dispense study drug bottle to participant after filling in label on bottle with: (scheduled follow up drug dispensed at this visit as per protocol)
 - Bottle ID:
 - Date Dispensed
 - Physician
 - Emergency study contact #
 - Patient Name
 - Expiration date
 - Study drug directions for use
- *Note: use a ballpoint pen when writing on the bottle label.
- After visit
 - Enter remaining forms and questionnaires into TRIM data system within 10 working days.

Forms (abbreviation)

- Clinic Visit (CV)
- Drug Dispensing (DA), if needed
- Drug Return/Tablet Count (DR)
- Pulmonary Function Testing (PF)
- TRIM Diary (DC) Cards
- Physical Measurements (PM)
- Suicide Severity Screener (SSW)*, if needed
- Treatment Termination (TT), if needed

Questionnaires (abbreviation)

- Asthma Symptom Utility Index (AS) (coordinator completes)
- Asthma Control Test (TA)
- Marks Quality of life questionnaire (MQ)
- Quality of Life Questionnaire (SF)
- Gastrointestinal Symptom Rating Scale (GS)
- Patient Health Questionnaire for Depression and Anxiety (HQ)

Log/Administrative forms (abbreviation)

- Unanticipated Problem (UP) or Serious Adverse Event (SR), if needed
- Early Study Exit (EE), if needed
- Medications Log (non-asthma/non-allergy) (CM) (entered into database after final study visit)
- Asthma and Allergy Medications Log (AA) (entered into database after final study visit)

* Not data entered

2.5. Follow up visit (V5)

Overview

V5 includes questionnaires, assessment of adverse events, spirometry, interim health history, pregnancy test (if applicable), blood pressure, anthropometrics, and pill counts. Participants will be given TRIM Diary (DC) Cards to be filled out daily and returned at V6.

Time frame

- Target- 12 weeks after randomization (V2)
- Window- 11-13 weeks after V2
- Duration- 1 to 1 ½ hours

Equipment/materials

- V5 forms and V5 checklist
- Spirometer
- Pregnancy test (for females of childbearing potential)
- Extended tape measure
- Automated blood pressure cuff

Tasks

- Pregnancy test (for female participants of childbearing potential)
 - If test is positive STOP, participant is no longer eligible, fill out a Treatment Termination (TT) form and instruct participant to return study drug
- Check weight, and waist and hip circumference (PM)
- Blood pressure measurement (PM)
- Drug Return/Tablet Count
 - Complete Drug Return/Tablet Count (DR) form
 - Count tablets and record on form. Tablets should be counted at least twice, or until results can be repeated (Count tablets using gloves and pill counter in front of participant)
 - Determine approximate expected number of remaining tablets and compare to actual number returned
- Questionnaires
 - Coordinator completes Asthma Symptom Utility Index (AS) with participant's input
 - Have participant complete:
 - Asthma Control Test (TA)
 - Marks Quality of Life Questionnaire (MQ)
 - Quality of Life Questionnaire (SF)
 - Gastrointestinal Symptom Rating Scale (GS)
 - Patient Health Questionnaire for Depression and Anxiety (HQ)
- Administer the Suicidality Severity Screener (SSW) form if participant scores greater than 0 on item 9 of the Patient Health Questionnaire for Depression and Anxiety (HQ)
 - If the total PHQ-9 score (item 10) is 15 or more or the total GAD-7 score (item 19) is 10 or more, or if there is a change in score totaling 5 or more, from baseline (V2), participant should be given mental health resource information.

- Complete forms and procedures:
 - Clinic Visit (CV) Form, includes interim medical history and study drug dose and tolerability
 - Medications Log (non-asthma/non-allergy) (CM)
 - Asthma and Allergy Medications Log (AA)
 - Pulmonary function testing (PF) form- collect pre- bronchodilator PFT data; results are recorded on the pulmonary Function Form (PF). Printout of spirometry session to be stored as source documentation
 - Review TRIM Diary (DC) Cards with participant and guide participant to make edits if any are required
 - Screen for adverse events.
 - Distribute and review
 - TRIM Diary (DC) Cards to be brought back at V6
 - ACRC appointment card for V6
 - Dispense study drug bottle to participant after filling in label on bottle with: (scheduled follow up drug dispensed at this visit as per protocol)
 - Bottle ID:
 - Date Dispensed
 - Physician
 - Emergency study contact #
 - Patient Name
 - Expiration date
 - Study drug directions for use
- *Note: use a ballpoint pen when writing on the bottle label.
- After visit
 - Enter remaining forms and questionnaires into TRIM data system within 10 working days.

Forms (abbreviation)

- Clinic Visit (CV)
- Drug Dispensing (DA), if needed
- Drug Return/Tablet Count (DR)
- Pulmonary Function Testing (PF)
- TRIM Diary (DC) Cards
- Physical Measurements (PM)
- Suicide Severity Screener (SSW)*, if needed
- Treatment Termination (TT), if needed

Questionnaires (abbreviation)

- Asthma Symptom Utility Index (AS) (coordinator completes)
- Asthma Control Test (TA)
- Marks Quality of life questionnaire (MQ)
- Quality of Life Questionnaire (SF)
- Gastrointestinal Symptom Rating Scale (GS)
- Patient Health Questionnaire for Depression and Anxiety (HQ)

Log/Administrative forms (abbreviation)

- Unanticipated Problem (UP) or Serious Adverse Event (SR), if needed
- Early Study Exit (EE), if needed
- Medications Log (non-asthma/non-allergy) (CM) (entered into database after final study visit)
- Asthma and Allergy Medications Log (AA) (entered into database after final study visit)

* Not data entered

2.6. Follow up visit (V6)

Overview

V6 includes questionnaires, assessment of adverse events, spirometry, interim health history, pregnancy test (if applicable) blood pressure, anthropometrics, and pill counts. Participants will be given TRIM Diary (DC) Cards to be filled out daily and returned at V7.

Time frame

- Target- 18 weeks after randomization (V2)
- Window- 17 to 19 weeks after V2
- Duration- 1 to 1 ½ hours

Equipment/materials

- V6 forms and V6 checklist
- Spirometer
- Mini-Wright Peak Flow Meters
- Albuterol
- Pregnancy test (for females of childbearing potential)
- Extended tape measure
- Automated blood pressure cuff
- Instructions for Methacholine Challenge Test

Tasks

- Pregnancy test (for female participants of childbearing potential)
 - If test is positive STOP, participant is no longer eligible, fill out a Treatment Termination (TT) form and instruct participant to return study drug
- Check weight, and waist and hip circumference (PM)
- Blood pressure measurement (PM)
- Drug Return/Tablet Count
 - Complete Drug Return/Tablet Count (DR) form
 - Count tablets and record on form. Tablets should be counted at least twice, or until results can be repeated (Count tablets using gloves and pill counter in front of participant)
 - Determine approximate expected number of remaining tablets and compare to actual number returned
- Questionnaires
 - Coordinator completes Asthma Symptom Utility Index (AS) with participant's input
 - Have participant complete:
 - Asthma Control Test (TA)
 - Marks Quality of Life Questionnaire (MQ)
 - Quality of Life Questionnaire (SF)
 - Gastrointestinal Symptom Rating Scale (GS)
 - Patient Health Questionnaire for Depression and Anxiety (HQ)

- Administer the Suicidality Severity Screener (SSW) form if participant scores greater than 0 on item 9 of the Patient Health Questionnaire for Depression and Anxiety (HQ)
 - If the total PHQ-9 score (item 10) is 15 or more or the total GAD-7 score (item 19) is 10 or more, or if there is a change in score totaling 5 or more, from baseline (V2), participant should be given mental health resource information.
 - Complete forms and procedures:
 - Clinic Visit (CV) Form, includes interim medical history and study drug dose and tolerability
 - Medications Log (non-asthma/non-allergy) (CM)
 - Asthma and Allergy Medications Log (AA)
 - Pulmonary function testing (PF) form- collect pre- bronchodilator PFT data; results are recorded on the pulmonary Function Form (PF). Printout of spirometry session to be stored as source documentation
 - Review TRIM Diary (DC) Cards with participant and guide participant to make edits if any are required
 - Screen for adverse events.
 - Distribute and review
 - TRIM Diary (DC) Cards to be brought back at V7
 - ACRC appointment card for V7
 - Provide and review the Instructions for Methacholine Challenge Test with participant
 - If needed; dispense study drug bottle to participant after filling in label on bottle with:
(No follow up bottle dispensed at this visit based on protocol)
 - Bottle ID:
 - Date Dispensed
 - Physician
 - Emergency study contact #
 - Patient Name
 - Expiration date
 - Study drug directions for use
- *Note: use a ballpoint pen when writing on the bottle label.
- After visit
 - Enter remaining forms and questionnaires into TRIM data system within 10 working days.

Forms (abbreviation)

- Clinic Visit (CV)
- Drug Dispensing (DA), if needed
- Drug Return/Tablet Count (DR)
- Pulmonary Function Testing (PF)
- TRIM Diary (DC) Cards
- Physical Measurements (PM)
- Suicide Severity Screener (SSW)*, if needed
- Treatment Termination (TT), if needed

Questionnaires (abbreviation)

- Asthma Symptom Utility Index (AS) (coordinator completes)
- Asthma Control Test (TA)
- Marks Quality of life questionnaire (MQ)
- Quality of Life Questionnaire (SF)
- Gastrointestinal Symptom Rating Scale (GS)
- Patient Health Questionnaire for Depression and Anxiety (HQ)

Log/Administrative forms (abbreviation)

- Unanticipated Problem (UP) or Serious Adverse Event (SR), if needed
- Early Study Exit (EE), if needed
- Medications Log (non-asthma/non-allergy) (CM) (entered into database after final study visit)
- Asthma and Allergy Medications Log (AA) (entered into database after final study visit)

Instruction sheets (abbreviation)

- Instructions for Methacholine Challenge Test (IMC)

* Not data entered

2.7. End of treatment visit (V7)

Overview

The purpose of V7 is to document TRIM study drug treatment termination, return study drug to clinic, questionnaires, assessment of adverse events, methacholine challenge test, interim health history, pregnancy test (if applicable), blood pressure, anthropometrics, and a blood draw (this may be completed on a separate day, within 1 week of the actual V7 visit). Participants will return their TRIM Diary (DC) Cards and Study Medication Use forms, and receive an unmasking envelope and study exit letter.

Time frame

- Target- 24 weeks after randomization (V2)
- Window- 23 to 25 weeks after V2
- Duration- 1 to 2 hours

Equipment/materials

- V7 forms and V7 checklist
- Methacholine challenge test supplies, if $FEV_1 \geq 60\%$ predicted and $> 1.5L$
 - AeroEclipse II
 - Breath actuated nebulizer
 - Rotameter/precision flow meter
 - Easy On spirometer
 - Laptop
- Spirometry supplies if $FEV_1 < 60\%$ predicted and $< 1.5L$
 - Mini-Wright Peak Flow Meters
 - Albuterol (MDI or nebulizer depending on clinic's standard protocol)
- Specimen collection, processing and storage supplies
- Pregnancy test (for females of childbearing potential)
- Extended tape measure
- Automated blood pressure cuff
- Exit envelope (includes participant exit letter, sealed treatment unmasking envelope, and unmasking letter)

Tasks

- One-day prior, call participant to remind them about fasting blood draw, medication holds for the methacholine challenge test, and to bring study drug bottle to visit
- Pregnancy test (for female participants of childbearing potential)
 - If test is positive STOP, participant is no longer eligible, fill out a Treatment Termination (TT) form and instruct participant to return study drug
- Check weight, and waist and hip circumference (PM)
- Blood pressure measurement (PM)
- Questionnaires
 - Coordinator completes Asthma Symptom Utility Index (AS) with participant's input
 - Have participant complete:
 - Asthma Control Test (TA)
 - Marks Quality of Life Questionnaire (MQ)
 - Quality of Life Questionnaire (SF)
 - Gastrointestinal Symptom Rating Scale (GS)

- Administer the Suicidality Severity Screener (SSW) form if participant scores greater than 0 on item 9 of the Patient Health Questionnaire for Depression and Anxiety (HQ)
 - If the total PHQ-9 score (item 10) is 15 or more or the total GAD-7 score (item 19) is 10 or more, or if there is a change in score totaling 5 or more, from baseline (V2), participant should be given mental health resource information.
- Complete forms and procedures:
 - Clinic Visit (CV) Form, includes interim medical history and study drug dose and tolerability
 - Medications Log (non-asthma/non-allergy) (CM)
 - Asthma and Allergy Medications Log (AA)
- Methacholine testing (See separate Methacholine MOP)
 - If participant's $FEV_1 < 60\%$ predicted and $< 1.5L$, spirometry should be performed instead of the methacholine challenge test
- Review TRIM Diary (DC) Cards with participant and guide participant to make edits if any are required
- Fasting blood draw: patient should fast from midnight and blood should be collected prior to 11 am. Participant may eat and drink after blood is collected.
- Screen for adverse events.
- Complete Unmasking form (UM)
- Collect remaining drug from participant
- Drug Return/Tablet Count
 - Participant to return used/partially used bottle
 - Complete Drug Return/Tablet Count (DR) form
 - Record bottle ID# on DR form
 - Count tablets and record on form. Tablets should be counted at least twice, or until results can be repeated (Count tablets using gloves and pill counter in front of participant)
 - Determine approximate expected number of remaining tablets and compare to actual number returned
- Give participant:
 - Exit envelope which includes
 - Participant exit letter (see prototype in MOP section 8.4)
 - Sealed treatment unmasking envelope
 - Unmasking letter (see Appendix G)
 - Copy of final spirometry results
 - Copy of final methacholine results
- After visit
 - Send physician exit letter (see prototype in MOP section 8.3) to participant's primary pulmonary physician
 - Enter data as recorded on forms and questionnaire into TRIM data system within 10 working days

Forms (abbreviation)

- Clinic Visit (CV)
- Biospecimen Collection (BC)
- Methacholine form (MC)
- Pulmonary Function Testing (PF), if needed
- Physical Measurements (PM)
- Drug Return/Tablet Count (DR)
- Treatment Termination (TT)
- Unmasking (UM)
- Study Evaluation (SV)
- Suicide Severity Screener (SSW)*, if needed

Questionnaires (abbreviation)

- Asthma Symptom Utility Index (AS) (coordinator completes)
- Asthma Control Test (TA)
- Marks Quality of life questionnaire (MQ)
- Quality of Life Questionnaire (SF)
- Gastrointestinal Symptom Rating Scale (GS)
- Patient Health Questionnaire for Depression and Anxiety (HQ)

Log/Administrative forms (abbreviation)

- Unanticipated Problem (UP) or Serious Adverse Event (SR), if needed
- Medications Log (non-asthma/non-allergy) (CM)
- Asthma and Allergy Medications Log (AA)

* Not data entered

2.8. Missed procedures

Time frame

- After time window has closed for a specified study visit and any of the following were missed:
 - All requirements for a visit
 - One or more of the procedures or forms required for a visit (missed data at a visit)

Tasks

- When scheduling a visit, attempt to schedule the visit at a convenient time, preferably early in the time window
- If the appointment needs to be rescheduled, keep it as early in the window as possible
- If you are unable to contact participant:
 - Attempt to contact all telephone numbers listed (work, home, cell) on Participant Information (PI) form
 - Make calls at different times of the day
 - Attempt to e-mail participant
 - Send a letter to participant
- Record specific missed forms and reason data and/or visit was missed on Missed Data (MD) form
- Record asthma diaries and Study Medication Use forms not returned as missing on a MD form
- Participants who have missed a visit
 - Once enrolled, a participant is never considered “off study” until after the scheduled follow-up period ends
 - A Missed Data (MD) form is required at the close of the V7 window
- Forms that are expected and required at baseline (V1 and V2) and are missing are to be reported as protocol deviations

Forms (abbreviation)

- Missed Data form (MD)
- Participant Information (PI)

2.9. Rescreening

Definition

- An opportunity to determine if a participant who previously did not meet eligibility criteria during screening at a V1 may meet eligibility criteria.
 - This include participants that were taking roflumilast or theophylline who needed to complete a 4 weeks washout.

Tasks

- For participants who were not able to meet eligibility criteria at screening (V1)
 - Keep initial V1 paperwork (screen failure) and keep on file
- At rescreening visit (rescreen at least 4 weeks after initial V1):
 - Repeat V1
 - Redo all V1 procedures and complete new set of V1 forms
 - **Use the same Participant ID number and Alpha ID code** (assigned at original V1)
 - Continue to save paperwork from previous visits (e.g., V1 “screen failure”)
 - Enter new forms into the database
 - Update Participant Screening Log (PS)

*Note: Participants may be re-screened one time.

Forms (abbreviation)

- All V1 forms, if applicable

Log/Administrative forms (abbreviation)

- Participant Screening Log (PS)

3. Treatment administration

3.1. Study drug

3.1.1. Study drug description

Roflumilast is an FDA approved drug for the treatment of recurrent exacerbations of Chronic Obstructive Pulmonary Disease (COPD). It has not been approved for asthma. Preliminary data support the efficacy of roflumilast for treatment of asthma. Roflumilast promotes weight loss, especially in obese individuals, and significant weight loss may improve asthma symptoms in this specific population. Study drug will be prescribed as follows:

- After randomization at V2 and every other day until V3
 - Masked study drug, one tablet every other day of roflumilast 500 µg OR placebo
- V3 continuing to V7:
 - Masked study drug, one tablet per day of roflumilast 500 µg OR placebo
 - Dose is only increased if participant tolerates the drug well (no or minimal side effects)
 - If participant does not tolerate drug, they will continue to take it every other day for the rest of the study
- Dosing instructions
 - Take study drug every other day starting at V2 to V3. If study drug is tolerated, increase dose to 1 tablet every day.
 - Do not make up a missed dose; do not double up dosing

3.1.2. Side effects of roflumilast

- The most common side effects of roflumilast include diarrhea, weight decrease, nausea, headache, back pain, influenza (flu), insomnia (difficulty sleeping), dizziness (dizzy), and decreased appetite.
- Most side effects generally happen in the first week of dosing and resolve with continued use.
- As with any drug, the participant may experience some discomfort or side effects associated with the use of the drug that have not already been reported.
- Roflumilast also comes with warnings about psychiatric side effects including insomnia, anxiety and depression. Instances of suicidal ideation and behavior, including completed suicides, were observed in clinical trials in individuals with COPD and no prior history of depression.
- **Weight loss is considered to be a positive outcome for this study population. If a participant loses ≥ 10% of baseline weight during the course of the trial, this should be discussed with the study physician (preferably the study PI) as soon as possible.**

3.1.3. Drug interactions

Roflumilast is metabolized by cytochrome 3A4 and 1A2 which includes the cytochrome P450 (CYP P450) enzyme. This enzyme decreases systematic levels of roflumilast with some drugs and increases levels with others. Therefore, all CYP P450 drugs are listed as drug interactions with roflumilast.

The following are drugs that participants should **not** be taking if they are participating in TRIM:

- Rifadin® (rifampicin)
- Luminal® (phenobarbital)
- Carnexiv® (carbamazepine)
- Dilantin® (phenytoin)
- Ery-Tab® (erythromycin)
- Nizoral® (ketoconazole)
- Tagamet® (cimetidine)
- Luvox® (fluvoxamine)
- Penetrex® (enoxacin)
- Femodene® (oral contraceptives containing ethinyl estradiol with gestodene)
 - Please note: These oral contraceptives are not available in the United States; please refer to the following link for drug list:
<https://www.drugs.com/international/gestodene.html>

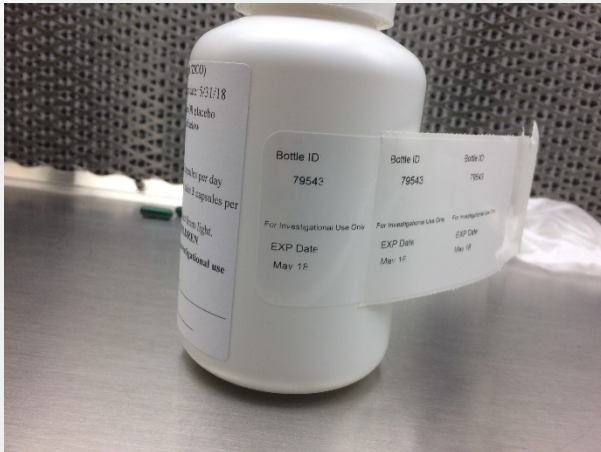
3.1.4. Receipt and drug distribution

All drugs will be packaged and distributed by the Temple University School of Pharmacy.

- DCC is responsible for coordinating the distribution of specific drug bottles to clinics, as well as ordering additional drugs for clinics, as needed.
- Lead Coordinator at each clinical site is responsible for maintaining records related to the receipt, issuance, and destruction of study drug.

Receipt of new drug from Temple

- Upon receipt of study drug from Temple University, the Lead Coordinator is responsible for reconciling the shipment log with the study drug bottles received.
- If there is a discrepancy, contact the DCC.
- Description of bottles:
 - 55 tablets of either study drug or placebo.
 - Each bottle will have a unique bottle ID.
 - The drug label will be perforated; one section of the label will be torn off on receipt and one section will be torn off when the drug is dispensed. Please see Drug Assignment section below.



Bottle of study drug with three-part perforated tear-off label.

Label 1: to be removed on receipt of study drug and placed on packing list (section 3.1.4.)

Label 2: to be removed on assignment of bottle to participant and attached to Drug Dispensing (DA) form (section 3.1.5.)

Storage

All study drugs are to be stored:

- In a secure, locked location with limited public access and in accordance with your institution's policies (e.g. study drug may be kept in your local pharmacy if required).
- At room temperature (68-77°F); excursions permitted to (59-86°F).
- With Bottle ID labels intact until assigned and dispensed to a participant.

Drug accountability

The shipment will include a packing list indicating each individual bottle. There are two steps the clinic coordinator is to take upon receiving a drug shipment:

- First, reconcile drug received with packing list:
 - Match each entry on the packing list with its corresponding bottle in the shipment.
 - Attach first tear off label from each bottle next to its entry on the packing list.
- Next, mark bottles as received in the database: Use the reconciled packing list to mark bottles as received in TRIM database, using the TRIM Drug Distribution System link and the Mark Kit(s) As Received link.
- Once both steps (reconciliation and marking bottles as received) are complete, the reconciled packing list is to be signed by the coordinator, and stored in the regulatory binder.
 - If drug is missing or bottles do not match the packing list, contact the TRIM Data Coordinating Center (JHSPH.ala-acrc@jhu.edu) as soon as possible.
- Missing drug (lost at site, not lost by participant) should be reported as a protocol deviation on an Unanticipated Problem (UP) form.

Disposition of returned, unused, and expired drug

- Unused study drug is to be returned to Temple University for destruction.
- Ship drug back to Temple using a Chain of Custody form supplied by Temple University.
- Drug that is returned from participants is to be returned to Temple University for destruction.
- It is extremely important that return tablet counts are verified before remaining drug is shipped to Temple.
- Expired drug, that was not dispensed, is to be returned to Temple University for destruction after replacement drug has arrived.

3.1.5. Drug assignment and dispensing

All randomized participants will receive a bottle containing 55 tablets at V2.

- **Note: No two bottles will have the same Bottle ID#.**

V2- Randomization to treatment

To obtain a bottle assignment at randomization:

- The following forms must have been keyed into the TRIM data system:
 - Screening (SC) form
 - Eligibility (EL) form
- Complete treatment assignment:
 - In Data System menu, select TRIM Treatment Assignment (Randomization) link
 - Enter participant information
 - Print out treatment assignment generated by the TRIM data system; store in participant's research record
- Document treatment assignment:
 - Attach tear- off label to Drug Assignment and Dispensing (DA) form
 - Data enter the DA form at the time of the visit

Important: Data entry of the drug assignment verifies that the correct treatment was dispensed to the participant.

- Drug label (attached to the bottle), fill in with a ballpoint pen:
 - Bottle ID:
 - Date Dispensed
 - Physician
 - Emergency study contact #
 - Patient Name
 - Expiration date
 - Study drug directions for use

3.1.6. Study drug dosing schedules

3.1.6.1. Normal dispensing schedule: Every other day for 2 weeks; every day if tolerated

Visit	V2	V3	V4	V5	V6	V7
Window	0 weeks	2 weeks	6 weeks	12 weeks	18 weeks	24 weeks
Bottle number dispensed	1	N/A	2	3	N/A	N/A
Pills taken	0	7	28	42	42	42
Pills remaining	55	48	20 + 55	33 + 55	46	4
Total pill count	55	48	75	88	46	4
Bottle number returned	N/A	N/A	N/A	1 (V2 bottle)	2 (V4 bottle)	3 (V5 bottle)

3.1.6.2. Every other day dispensing schedule

Visit	V2	V3	V4	V5	V6	V7
Window	0 weeks	2 weeks	6 weeks	12 weeks	18 weeks	24 weeks
Bottle number dispensed	1	N/A	N/A	2	N/A	N/A
Pills taken	0	7	14	21	21	21
Pills remaining	55	48	34	13 + 55	47	26
Total pill count	55	48	34	68	47	26
Bottle number returned	N/A	N/A	N/A	1 (V2 bottle)	N/A	2 (V5 bottle)

3.1.7. Study drug return and count

- Participant will bring the study drug bottle back with them to each clinic visit
- Coordinator will wear gloves, use a pill counter, and count out drug in front of the participant
- Record the number of tablets on the Drug Return/Capsule Count Form (DR) and return the bottle to the participant
- If participant tolerates study drug, they should receive a new bottle at V4 and V5; instruct them to use the opened bottle first and to bring back the empty bottle to the next clinic visit
- At V7, participant will return all study drug to the clinic
 - If they forget, they must return as soon as possible (bring back to clinic, mail, etc.)

3.2. Unmasking of treatment assignment

Overview

Masked treatment is critical to the study design. Participants and clinic staff are to remain masked, except for extenuating circumstances. If unmasking is necessary during a participant's time in TRIM, it is important to limit the number of individuals who are unmasked. Ideally, site staff are not unmasked.

Unmasking supplies

- DCC will provide a prototype unmasking letter (see Appendix G), the letter must be reviewed and approved by local IRB prior to use.
- DCC will send each clinic sealed treatment unmasking envelopes
- Unmasking envelope has unique envelope ID and verification code on the front of the envelope
- Upon receipt of the unmasking envelopes, the clinic is to store them in a secure location, with access limited to TRIM study team members, until study closeout. **These envelopes are to remain sealed.**

3.2.1. Routine unmasking

When

- At V7, after all study data are collected for the participant, or
- After the V7 window is closed for the participant who missed V7

Procedure for unmasking at V7 or after

- All data should be collected prior to unmasking as well as study drug
- Access TRIM data system website to obtain the unmasking envelope ID.
 - Data system will assign an unmasking envelope ID based on the participant's treatment assignment and envelopes assigned to the clinic.
 - If the site cannot locate the envelope with the specified ID, the coordinator should contact the DCC by phone.
- Record **both** the Unmasking envelope ID and the Verification code on Unmasking form (UM)
- **Sealed** unmasking envelope is given to the participant if V7 clinic visit is complete
 - Participant's ID should be written on the envelope before it is given to participant
- Unmasking (UM) form should be dated to reflect the actual date the envelope is mailed to or handed to the participant. It is important that the clinic staff remain masked:
 - Instruct participant to open the envelope **AFTER** leaving the visit
 - Study staff do **NOT** discuss the treatment assignment with the participant
 - Participant should share the treatment assignment with his/her PCP or asthma doctor (unless the provider is a TRIM study physician, in which case the participant should only share the treatment assignment with their PCP).
- If the V7 window has closed and no additional data will be collected, the envelope will be mailed to the participant. The participant's ID should be written on the sealed envelope when it is retrieved. The UM form should reflect the date the unmasking envelope is mailed.

Form

- Unmasking (UM) form

3.2.2. Emergency unmasking

Unmasking of treatment assignment prior to V7 should be limited to emergency situations, such as accidental ingestion by a child. If a participant experiences an adverse event that the study physician believes is possible caused by study treatment, study treatment should be stopped and the participant then treated according to best medical judgement. Unmasking is only necessary if knowledge of the treatment assignment will influence the care of the patient

Procedure for unmasking before V7

- During business hours (general, M-F 8:00-5:00 pm, Eastern Time) call DCC for emergency unmasking:
 - Gem Roy at 443-287-5796
 - Heather Hazucha at 410-502-0585
 - Bob Wise at 410-905-5688
 - Main number at 443-287-3170
- During non-business hours or if a DCC staff member is not available, use the data system link “Emergency Unmasking” to perform an emergency unmasking.
 - This will require the participant ID be data entered
- Make arrangements with the participant to return all study drug back to the clinic

Reporting requirements

- Depending on the reason for unmasking, the clinic should complete and submit an Unmasking (UM) form, **and**, if applicable, an Unanticipated Problem (UP) form or Serious Adverse Event (SR) form.
- If the reason for unmasking involves an unanticipated problem or Serious Adverse Event Report, the details should include:
 - The reason for emergency unmasking
 - Who requested the unmasking (name and title)
- All emergency unmasking will be reviewed by the TRIM DCC and the DSMB; improper use of the emergency unmasking system will be considered misconduct.

Form

- Unmasking (UM)

4. Clinic certification and study supplies

4.1. Clinic certification

Purpose

- Provide confirmation and documentation that the main ACRC Clinical Center and any satellite centers have obtained the required approvals, facilities, equipment, personnel, and training necessary to conduct TRIM.
- Ensure consistent conduct of study procedures over time within and across clinics
- Ensure that each ACRC clinical site has local IRB approval, and that all ICFs in use contain essential information related to conduct of trial.

When

Certification must be completed before an ACRC Clinical Center may recruit

Tasks

ACRC Clinical Center and satellite certification requires

- Informed consent form (ICF) for each clinical site (main and satellite) is to be approved by the DCC *before* submission to local IRB.
 - Modify prototype ICF (provided by DCC) to meet local requirements
 - Completed consent checklist and submit to the DCC
- Submission to local IRB
 - Protocol
 - Informed consent
 - Questionnaires
 - Recruitment and retention materials (e.g., appointment card)
 - Certificate of Confidentiality (CoC)
- Certification of site staff
 - All study staff must have an ACRC Personnel Assurance Statement on file
 - All staff must:
 - Review TRIM protocol and complete General Knowledge Assessment (GEN) on TRIM website
 - Complete a Personnel Certification (CE) form
 - Sign the TRIM Signature and Delegation of Authority Log
 - Complete role specific certification requirements (see Section 4.3)
- Completion of the Clinic/Satellite Certification forms
 - Clinic Certification (CC) form completed by the main ACRC Clinical Center
 - Assurance that facilities, equipment, and supplies that are needed to conduct TRIM procedures are at the site.
 - Completion of Satellite Certification form (CT) by each satellite center; reviewed by Lead Coordinator of main ACRC Clinical Center
- Submission to DCC
 - IRB's notice of protocol approval (copy of notification is sufficient) and
 - Copy of each approved consent statement (with the stamp of approval, if applicable)
 - Signature and Delegation of Authority Log
 - Staff certification materials

4.2. IRB approval and informed consent

Tasks

- Create ICF in accordance with institution's IRB guidelines
 - Use TRIM model consent as a guide
 - Use checklist to be sure all ACRC required elements have been included
- Get DCC approval of consent *prior* to IRB submission
 - Use comment boxes in Word to indicate where all required consent checklist items are located in ICF.
 - Submit checklist and marked ICF to DCC for pre-approval
- Submit DCC approved ICF and TRIM protocol to institution's IRB for approval; submit other study documents which require IRB approval (e.g., questionnaires, recruitment materials, CoC)
- Submit approved and stamped ICF and IRB approval letter for protocol to DCC with certification materials.

4.3. Staff certification

Purpose

- All site study staff working on TRIM are required to be certified. This includes the PI/Center Director, coordinators, data entry staff, and spirometry testers.

Tasks

- Completion of General Knowledge Assessment (GEN)
- Signed ACRC Personnel Assurance Statement (PA)
- Complete a Personnel Certification (CE) form
- Sign and date TRIM Signature and Delegation Log
- Complete additional certification for specialized tasks (e.g., data entry, spirometry, methacholine challenge test)

4.3.1. General certification requirements

- Individual staff
 - Personnel Assurance Statement
 - All staff participating in ACRC trials are to have signed an ACRC Personnel Assurance (PA) statement
 - PA should be signed **before** staff member is entered in the ACRC Directory
 - Personal Identification Number (PIN)
 - Lead Coordinator is responsible for assuring that *all study staff* are entered in the ACRC Directory.
 - ACRC Personnel Assurance Statement should be signed by study staff member before being entered in the ACRC Directory
 - An individual PIN is then assigned by the system along with a temporary password ("changeme")
 - A PIN is required before an individual can take the online assessments for certification

- Certification requirements for all TRIM staff
 - Study staff roles- these roles must be filled before a site can be certified; staff members can fill multiple roles
 - Center Director/PI- responsible for conduct of trial
 - Study physician- responsible for evaluation of participant (directly or through delegation and oversight)
 - Psychologist/licensed psychologist- used as a resource for the PI if a participant presents with elevated depression, anxiety, or suicidal thoughts
 - Coordinator(s)- responsible for completion and documentation of clinic visits, review of forms, questionnaires and asthma diaries
 - Spirometry Tester(s)- Technician for lung function testing
 - Methacholine Challenge Tester(s)-Technician for lung function testing
 - Data System Operator (DSO)- data entry
 - General Knowledge Assessment (TRIM GEN); a score of at least 80% is required to pass
 - TRIM GEN is based on the study protocol
 - To access the GEN:
 - Go to the TRIM website homepage
 - Click on Certification: Knowledge Assessments
 - Log in using your PIN and password (if this is your first log in, use the password “changeme”, you will then be prompted to choose your own password)
 - Follow the on-screen instructions to complete the test
 - When test is passed, print out results page. A copy of the results is submitted to the DCC along with other relevant certification materials.
 - **Note: The GEN can be repeated an unlimited number of times and is open book**
 - The assigned psychiatrist/licensed psychologist should take the general knowledge assessment. Please email the DCC if you have any issues.
 - Training in Good Clinical Practice
 - Familiarity with ACRC study procedures and form completion
 - Signature and Delegation of Authority Log
 - Each site staff member involved with TRIM is to sign and date the log
 - PI/Center Director to initial log to indicate delegation of duties
 - Log is updated if roles and responsibilities change
 - Up-to-date log to be submitted with each staff member’s certification packet

4.3.2. ACRC Spirometry Tester Certification

Objective

- If previously certified as Spirometry Tester for concurrent ACRC trail (e.g., COCO), additional certification is not required
- Certification requires the individual being certified to complete:
 - 3 spirometry sessions
 - Sessions to be performed on ACRC study subjects or healthy volunteers (but not study staff)
 - Spirometry reports should have person seeking certification listed as the technician. Spirometry sessions are to be supervised until the individual is fully certified.
 - The report for each session being submitted:
 - **ID:** To identify the test (the “participant ID”) use an ID that includes:
 - Clinical site’s assigned study letter
 - Number between 900-999
 - For example, IB952
 - Use different ID for each test
 - **Tech (technician):** Use Spirometry Tester’s ACRC PIN
 - **Comments/Visit ID:** Use V0 for certification. Also include any other important information, such as who supervised test if done for certification.
 - The email should indicate the sessions are to be graded for ACRC Spirometry certification
 - Submit to the DCC:
 - Completed TRIM Pulmonary Function Testing (PF) form for one spirometry session (from one of the above spirometry sessions)
 - Spirometry session report (spirometry report from the spirometer showing correct settings and all efforts performed)
 - Copy of Signature and Delegation of Authority Log with required information completed for individual requiring certification
 - Print out of on-line calculator for spirometry used for PF
 - Submit all of the above, along with updated Signature and Delegation of Authority (SD) Log, to the DCC via email at JHSPH.ala-acrc@jhu.edu
- Certification is not complete until the DCC notifies the site of the individual’s successful certification.

Grading of spirometry

The reviewer will determine acceptability and assessment of the overall session as noted below.

FVC and FEV₁

The spirometry reviewer will assign grades for flow (FEV₁) and volume (FVC) and will provide an assessment of the overall session as follows:

Grade	Criteria
A	Repeatability 0.00L - 0.10L
B	Repeatability 0.11L - 0.15L
C	Repeatability 0.16L - 0.20L
D	Repeatability >0.20L

Assembly Assessment

Assessment	Criteria
Excellent	At least 3 acceptable maneuvers; two repeatable (i.e. grade of A or B for both FVC and FEV ₁)
Good	8 maneuvers attempted if unacceptable or not repeatable
Fair	Fewer than 8 maneuvers attempted but at least 1 acceptable
Unacceptable	0 acceptable maneuvers

Forms

- SD
- CC
- PF

Log

- Signature and Delegation of Authority Log (SD)

4.3.3. Methacholine certification

- Refer to Methacholine MOP

4.3.4. Data systems certification

Access to the TRIM data system is restricted to ACRC Clinical Center staff certified for data entry.

Each ACRC Clinical Center is required to have at least one person certified for data entry for TRIM, although having more than one person certified is advised.

Staff members who were certified as data system operators from previous ACRC studies do not have to repeat DSO certification for TRIM.

Tasks for becoming a Data System Operator for TRIM are:

- Complete ACRC Personnel Assurance Statement (PA), if not already on file at site
- If new to ACRC, the Lead Coordinator must enter this person into the ACRC Directory; a PIN is assigned when the person is added to the Directory
- Review the TRIM data forms
- Complete online assessments:
 - TRIM General Knowledge test (GEN)
 - Data System Operator (DSO) Knowledge Assessments online and print results
 - Data entry of practice forms
 - Under data system, click on Certification Data System
 - Follow instructions, including entry of the practice forms, (submit print out of the successful completion of each to the DCC with other certification materials)
- The Lead Coordinator is to submit the following (as a complete packet) to the DCC
 - Printouts from the practice data entry “tests”
 - DSO Knowledge Assessment result
 - PA (if not previously submitted to the certification coordinator at the DCC)
 - Copy of updated (and signed) Signature and Delegation of Authority Log
- Data Coordinating Center will notify Lead Coordinator of completion of certification and activation for TRIM data entry

Accessing the TRIM data system

- Accessed via the internet using Microsoft Internet Explorer (version 5.0 or higher) on a PC running Microsoft Windows. The website must be accessed using Compatibility View.
- The webpage is <http://www.jhcct.org/Secure/TRIM/TRIMHome.asp>
 - **Note: Access to any part of the TRIM Data System requires a PIN and password as well as activation by the DCC.**
- First time data system is access using a PIN the password default is “changeme”
 - The system will instruct the user to create a unique password the first time that user logs in to the data system.
 - From that time forward, only the user’s unique password will work
 - The Lead Coordinator can reset a password if it is forgotten
- Each attempt to access any part of the data system will lead the user to a login screen, requiring a Clinic ID, PIN, and password.

4.3.5. Asthma Diary Card certification

- Certification requires the individual being certified to complete:
 - Both sample Scenarios of TRIM Diary Cards (DC) (see Instructions for TRIM Diary Cards (IDC) and Section 7.4.2. on how to correctly complete a TRIM Diary Card (DC))
 - Coordinator should complete two one-week TRIM Diary Cards (DC) based on scenarios 1 and 2 provided by the DCC and can be found on the TRIM website. Complete TRIM Diary Cards (DC) approximating the experience of a participant.
 - When filling out the participant ID for each scenario, make the last character an odd or even number. This will correspond with Scenario 1 or 2.
 - Make sure to fill out the Diary Card completely as if you were a participant. All required items should be filled in
 - After completing the TRIM Diary Cards (DC) as a participant, review as a coordinator and complete the rest of the TRIM Diary Card (DC)
- Submit to the DCC:
 - Completed TRIM Diary Cards (DC) from scenarios 1 and 2
 - Copy of Signature and Delegation of Authority Log with required information completed for individual requiring certification
 - Submit all of the above, along with updated Signature and Delegation of Authority (SD) Log, to the DCC via email at JHSPH.ala-acrc@jhu.edu
- Certification is not complete until the DCC notifies the site of the individual's successful certification.

4.4. Clinic responsibilities

Tasks

- Obtain IRB approval for protocol, consent, questionnaires and all recruitment materials
- Ensure that staff are trained and certified (physicians, coordinators, spirometry testers, and data entry personnel)
- Submit TRIM consent and completed Consent Checklist to the DCC prior to IRB submission
- Each ACRC Clinical Center should review and submit all materials for their satellite clinics
 - **Note: Each clinic must receive notification of clinical center and staff certification from the Data Coordinating Center (via email). Clinics cannot perform screening visits (V1) until they have received written notification of certification.**

4.4.1. General site requirements

Facilities

- Private area to conduct health interviews, to assess for eligibility, and to provide patient education
- Secure area for storage of study supplies, documents, and forms

Provided by the Clinical Center

- A computer meeting the following requirements for data entry
 - Microsoft Windows
 - Microsoft Internet Explorer (version 5.0 or higher)
 - Adobe Acrobat Reader 5.0 or above (available free from www.adobe.com)
 - Printer (recommended)
- Spirometer to measure FEV₁ and FVC
- Equipment to measure height and weight
- A tape measure to measure waist and hip circumference
- Gloves

General study supplies

- Section 4.4.2. list supplies needed to conduct trial, and how supplies are obtained

Forms (abbreviation)

- Clinical Center Certification (CC), 1 per site
- Satellite Certification (CT), 1 per satellite
- ACRC Personnel Assurance Statement (PA), 1 per study staff member
- Pulmonary Function Testing (PF), 1 for each person seeking spirometry certification
- Spirometry Assurance Statement (SA), 1 per site
- Methacholine Challenge Test Assurance Statement
- Signature and Delegation of Authority Log (SD), 1 per site

4.4.2. Study supplies

Data Coordinating Center will distribute the following:

- ACRC general supplies, found on ACRC General Supply order (GO) form
 - Labels for clinic contact information for participant folder
 - Magnets with ACRC logo
 - ACRC tote bag
 - ACRC appointment cards
- Participant supplies, found on TRIM Supply order (IO) form
 - Clinic label sheets (Participant IDs)
 - Folder for participant with TRIM cover
 - Wallet cards
 - Shippers (for biospecimens)
 - Labels for shipping of biospecimens and use of Dry Ice
 - Biohazard bags
 - Absorbent sheets
 - Vacutainer tubes
 - Micronic 96-well plates with 1.4 mL vials for aliquots (biorepository)
 - Empty micronic 96-well plates
 - 10 mL tiger top aliquot tubes
 - Pipettes
 - Peak flow meters
 - Disposable mouth pieces
 - Spirettes

Ordering additional supplies from Data Coordinating Center

- Order supplies, as needed
- Complete TRIM Supply order (IO) form or ACRC General Supply order (GO) form
- Requests should include number of items and date needed
- Fax or email to DCC

Clinical Centers will provide

- Spirometer and single use spirometer supplies (including filters and nose clips)
- Study forms and questionnaires (download from TRIM website
<http://www.jhcct.org/Secure/TRIM/TRIMHome.asp>)
- Gloves (for universal precautions with biospecimens)
- Dry ice for shipment of biospecimens

Forms (abbreviation)

- ACRC General Supply Order Form (GO)
- TRIM Supply Order Form (IO)

4.4.3. Participant folders

Purpose

- Provide participants a place for Asthma Diaries packets and other related study materials

When

- V1 (Screening)

Supplies

- 2 pocket folder with tangs and TRIM cover
- Labels, information labels for folders

Instructions and materials included

- Information label- attach on front of inside pocket. Use labels provided by DCC to customize the folder; print out to include ACRC Clinical Center's name, address, and contact information, such as name of TRIM coordinator, Study Physician name, and daytime and after hours phone numbers for clinic.
- TRIM Diary (DC) Cards- fill out dates for asthma Diary Card packets to cover entire study (24 weeks) plus 2 additional weeks as backup.
 - Clinics can create pre-filled TRIM Diary (DC) Cards
 - Fill out Day, Date, and Participant ID on each page of TRIM Diary (DC) Card
- Spare TRIM Diary (DC) Cards- include 1 packet that has not been prefilled with days and dates

Forms and instruction sheets

- TRIM Diary (DC) Cards

5. Procedures

5.1. Spirometry

5.1.1. Spirometry procedures

Purpose

- Measure FEV₁ (the amount of air expired in the first second during a forced expiratory maneuver) and FVC (forced vital capacity)

When

- Pre- and post-bronchodilator at V1, and just pre-bronchodilator at V3, V4, V5, and V6. Pre-bronchodilator spirometry should also be performed at V2 and V7 if not performing methacholine challenge.
 - **Note:** Proceed with spirometry testing even if participant indicates they have taken short or long acting bronchodilator prior to the clinic visit. Make sure to indicate whether they have taken either medication on the Pulmonary Function (PF) form (item 8).

Standardization of spirometry

- Equipment and procedures are based on the ATS recommendations for accuracy and precision
- All personnel performing spirometry should either be certified pulmonary function technologists (National Board of Respiratory Care) or receive sufficient instruction from qualified instructors to perform the procedure according to acceptable standards
- All sites will use Hankinson standards on spirometer available at site
 - Objective: The certification process is designed to show that the individual is able to both:
 - Coach a participant so as to obtain good to excellent results that are repeatable and reproducible and to
 - Accurately complete the Pulmonary Function Testing (PF) form
- The EasyOn spirometer needs calibrated by doing a single flow check before each test and a multi-flow check once a week.

Certification

- Requirements for certification as a Spirometry tester are covered in Section 4.3.2.

Predicted outcomes

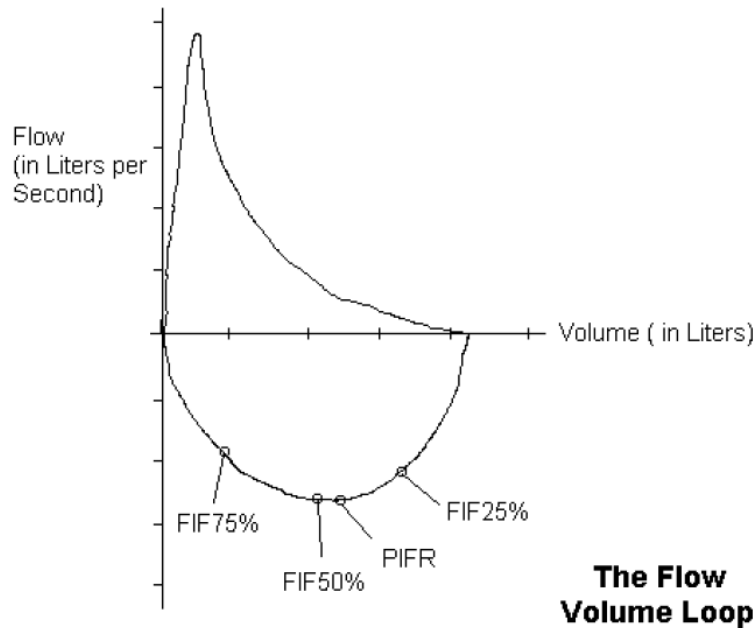
- Calculated according to the published predicted values (Hankinson et al). Calculate online using the TRIM pulmonary function calculator on the TRIM website:
<http://www.jhcct.org/Secure/TRIM/TRIMHome.asp>
 - **Note: Even if your spirometry system can be programmed to use the Hankinson (NHANES III) predicted values, note that your reports may print numbers for the predicted and percent predicted values that are not the same as the official ACRC values due to differences in rounding and calculation. ACRC clinics must use the exact values as reported by the online calculator. If your spirometry system can be programmed and verified to give exactly the same values as the online calculator, it will not be necessary to use the online calculator for each participant visit.**

Participant preparation

- Participant is seated with feet flat on floor
- Participant is wearing nose clips
- Restrictive clothing is loosened

Testing procedure

- Instruct the participant and demonstrate procedure
 - Lips should be sealed around the mouthpiece
 - Emphasize the necessity for deep and full inspiration, a hard and forceful expiratory “blast”, a complete expiration for at least 6 seconds, and finally a forceful inspiration following the expiration. (It is acceptable to do forced inspiration before the forced expiration, if equipment requires, but forced inspiration should follow forced expiration whenever possible.)
- Acceptability criteria
 - **Test start:** The peak flow should be sharp on FV (Flow Volume) curve. Participants may need coaching to get this right (i.e., BLAST it out)
 - **Cough:** Reject test when cough is within the first one second (FEV₁ will not be accurate). Cough in the later part of the VC is not a reason per se to reject the effort. Often, cough can be reduced by asking the participant to exhale SLIGHTLY less forcefully
 - **End of Expiration:** An acceptable expiratory effort should last at least 6 seconds (refer to volume time curve). Participants with severe obstructive lung disease may continue to exhale for 10 or more seconds. Occasionally, premature glottis closure causes abrupt test end. Participants may need to relax and try again with slightly less than maximum effort
- Reproducible criteria
 - **Definition:** Using the two criteria of FVC and FEV₁ to determine how well each acceptable effort compares with the largest acceptable effort
 - **FVC:** The second largest FVC should be within 0.15 L of the largest acceptable FVC
 - **FEV₁:** The second largest FEV₁ should be within 0.15 L of the largest acceptable FEV₁
- At least 3 acceptable and 2 reproducible efforts should be obtained. If this cannot be obtained after approximately 8 attempts, then the testing should be halted
- Time to peak flow, back extrapolation volume, and total expiratory time can be used to further assess the quality of each maneuver and overall test session
 - **Note: Inspiration is not required but is shown in figure of FV curve below**



Pre-bronchodilator (BD) procedures-

- Perform pre-bronchodilator spirometry on participant
 - Spirometry should be performed before any bronchodilators are used
 - Short-term bronchodilator should be held for 4 hours prior to testing
 - Recorded results on the Pulmonary Function Testing (PF) form
 - Pre-bronchodilator FVC
 - Pre-bronchodilator FEV₁

Post-bronchodilator (BD) procedures- only performed if required for eligibility

- Administer bronchodilator
 - Administer 2 puffs of metered dose inhaler (MDI) albuterol (with spacer or chamber)
 - When each puff inhaled, breath should be held for 5-10 seconds
 - Puffs should be done approximately 30 seconds apart
 - If participant needs an extra dose of albuterol, administer 2 more puffs
 - Wait 15-20 minutes after administering bronchodilator before retesting
- Perform post-bronchodilator spirometry
 - Record results on Pulmonary Function Testing (PF) form
 - Post-bronchodilator FVC
 - Post-bronchodilator FEV₁

Results

- Use online TRIM calculator to calculate pre- and post-bronchodilator percent predicted FEV₁ and post-BD FEV₁/FVC ratio
 - Record results on Pulmonary Function Testing (PF) form
 - Print out calculations and store as source document in participant's study binder

Documentation

- Complete the Pulmonary Function Testing (PF) form as you prepare for and during the session
- Determine FEV₁ percent predicted value:
 - Use TRIM online calculator from TRIM website:
<http://www.jhcct.org/Secure/TRIM/TRIMHome.asp>
 - Follow link to data system page and then to the TRIM calculator
- Note: The predicted values determined automatically by the Koko software are NOT acceptable. You must use the online calculator or the manual method above.

- Important: To reduce the risk of lost or missing data
 - Manually save results of pre-BD and post-BD test series
 - Print spirometry report at the time of the test; if no printer is available, create PDF of the report
 - Print results of the calculations (online TRIM calculator)

- Record the largest acceptable FEV₁ and FVC values on the PF form. These do not have to be taken from the same maneuver

Forms

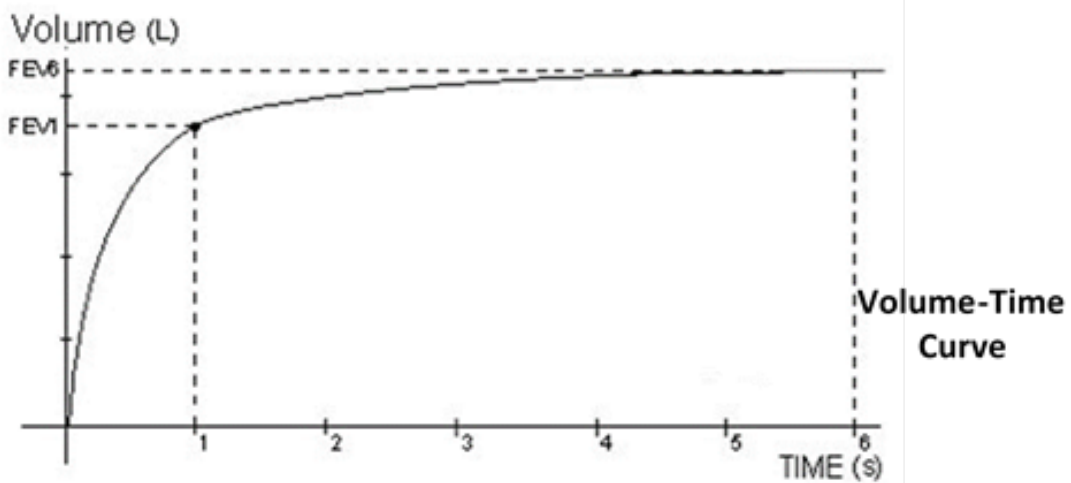
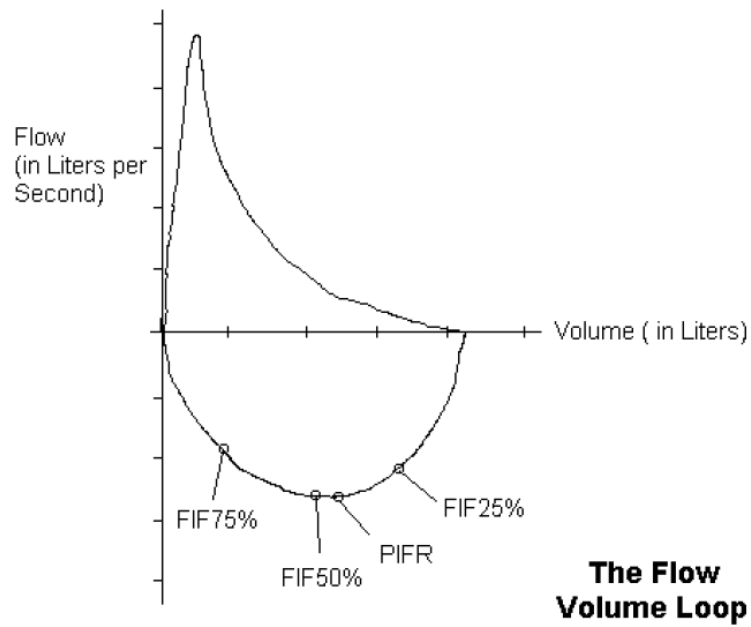
- Pulmonary Function Testing (PF)
- Screening Form (SC)

References

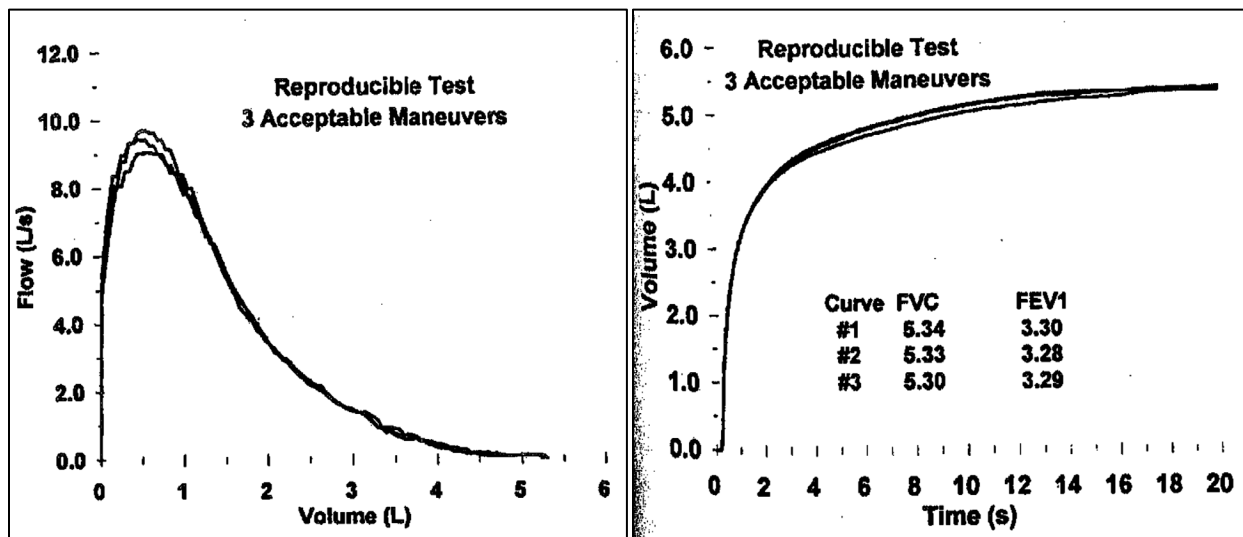
1. Hankinson, JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. Am J Resp Crit Care Med 1999; 159: 179 – 187
2. Standardization of Spirometry - 1994 update. American Thoracic Society. Am J Resp Crit Care Med 1995; 152: 1107 – 1136
3. Enright PL, et al. Spirometry in the Lung Health Study. Am Rev Resp Dis 1991; 143: 1215 – 1223
4. Lung Function Testing: Selection of Reference Values and Interpretive Strategies. American Thoracic Society. Am Rev Resp Dis 1991; 144: 1202 – 1218

5.1.2. Spirometry curves

Ideal curves

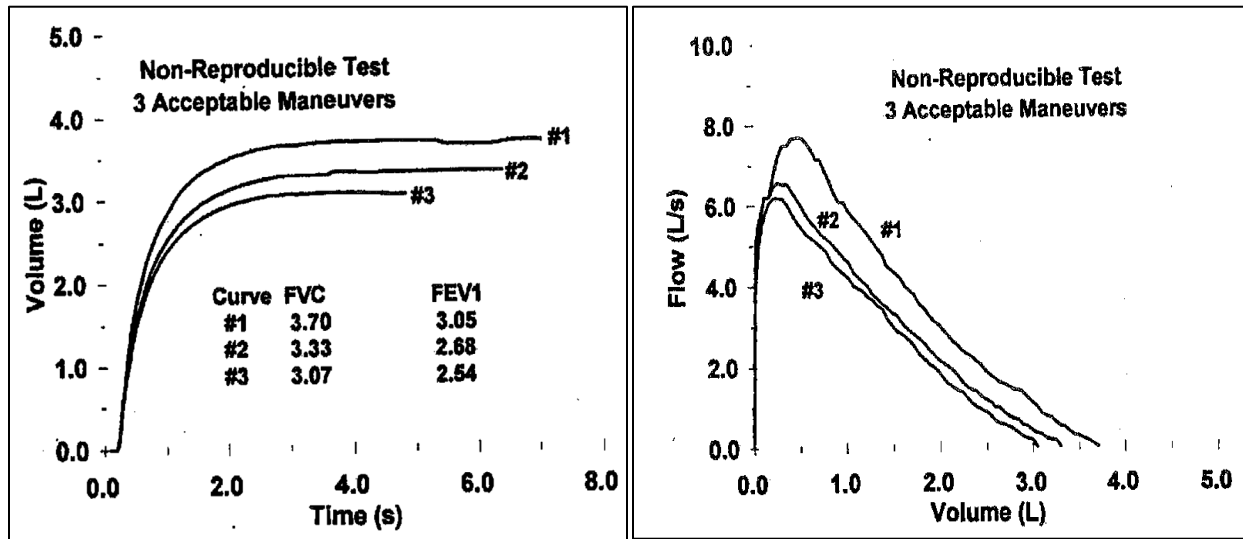


Acceptable and reproducible maneuvers



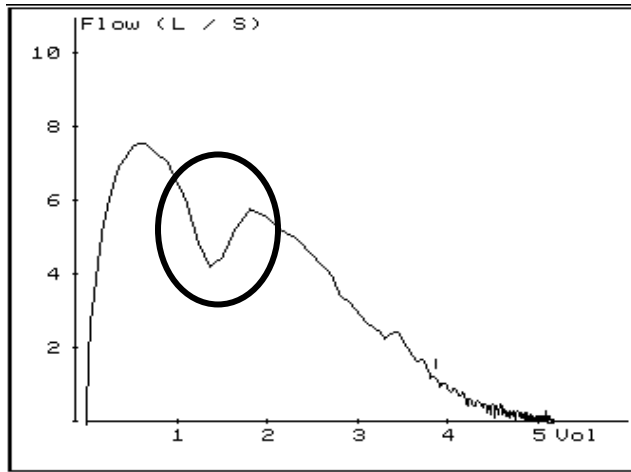
- Reproducible test with three acceptable flow-volume curves

Acceptable non-reproducible maneuvers

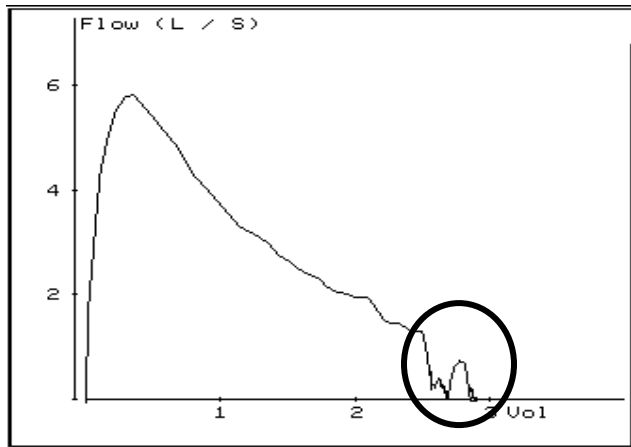


- Non-reproducible test with three acceptable flow-volume curves

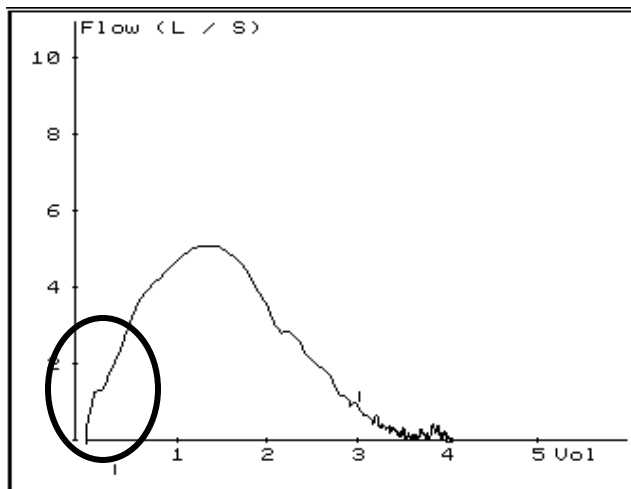
Maneuvers that are NOT acceptable



Cough
Flow-volume tracing



Abrupt termination
Flow-volume curve



Slow start
Flow-volume curve

5.2. Blood draws

Timing for blood draws

- Visits 2 and 7 require a fasting blood draw.
- Between 6 and 11 am, with the participant fasting from midnight (participant may drink water)
- Blood draw may be performed on a separate day from other procedures (within 7 days of the other procedures).
 - When blood draw is complete, send a sample to your local lab for glucose testing and process remaining for serum storage. See section 5.4.

Fasting blood glucose readings/instructions

Measurement	Steps to be taken by clinical staff*
< 100 mg/dL	No action
100-125 mg/dL	Notify participant and PCP within 3 months
126-199 mg/dL	Notify participant and PCP within 5 working days
200-299 mg/dL	Contact participant and PCP within 24 hours and complete a UP form
≥ 300 mg/dL	Contact participant and PCP urgently, to go to ED/PCP/urgent care and complete a UP form

*Note: Be sure to document in the participant's medical record when a clinical staff member informs them of their fasting blood glucose reading.

- Please see the example letter in Appendix F if the participant has an elevated fasting blood glucose reading.

5.3. Blood pressure

Equipment

- Vital signs monitor or automatic blood pressure cuff (cuff preferred)
- Use the same equipment at all visits for consistency
- Manual cuff, sphygmomanometer and stethoscope, only if automatic cuff is not available or if femoral BP is necessary
- Automatic cuff and manual blood pressure equipment should be inspected regularly, using manufacturer guidelines

Participant instructions

- Participants should not engage in vigorous exercise, ingest food or caffeine, or smoke within a half hour before the measurement
- Seat the participant with the arm supported at heart level, palm facing upwards, legs uncrossed, and the back supported
- Participants sit quietly for ten minutes before the first measurement
- Ask the participant if there are any reasons that the blood pressure cannot be done on either arm (sides)
- Remove all clothing that covers the location of the cuff placement
- Do not roll up the sleeve to expose the upper arm
 - If the upper arm cannot be exposed without constriction, place the cuff around the sleeve
- Neither the observer nor the participant should talk during the measurement procedure

Procedure

- Follow the manufacturer instructions for the specific cuff used at your site
- Follow the manufacturer instructions for the guidelines on cuff placement; however, in general, the bottom edge of the cuff should be 1 to 2 cm above the elbow with the marker centered on the middle of the inner arm
- Cuff size should be determined by measuring the participant's upper arm circumference and choosing the appropriate size which corresponds
- If the measurement cannot be taken from either arm, then a thigh, calf, or ankle may be used
- Measurements may be first recorded on the designated paper form and then entered into the database, or entered directly into the database

Blood pressure readings/instructions

Measurement	Steps to be taken by clinical staff*
Systolic: < 130 mmHg Diastolic: <85 mmHg	No action
Systolic: 130-159 mmHg Diastolic: 85-99 mmHg	Recommend participant discuss with their PCP
Systolic: > 160-179 mmHg Diastolic: > 100-119 mmHg	Consult the study physician
Systolic: > 180 mmHg Diastolic: >120 mmHg	Contact the study physician and recommend participant go to urgent care/ED.

*Note: Be sure to document in the participant's medical record when a clinical staff member informs them of their blood pressure readings.

Confidential, not for attribution or citation.

5.4. Specimen collection

Purpose

- Women of childbearing age will undergo pregnancy testing
- Fasting blood glucose will be collected and processed at each clinic's local lab
- Biospecimens (serum) will be collected for metabolic and oxidative markers (not optional) and future studies (optional)

When

- Pregnancy testing (urine) will occur at every clinic visit
- Blood will be collected at V2 and V7

5.4.1. Overview of specimen collection

Pregnancy testing (Required)

- Pregnancy testing will be done locally at all clinic visits. If participant has a positive pregnancy test at V1 or V2 they are NOT eligible.
- If participant tests positive at V3, V4, V5, V6, or V7, fill out a Treatment Termination form (TT)

Fasting blood glucose

- Fasting blood glucose will be taken at V2 and V7. This is not optional for the participant, and will be processed at each clinic's local lab.

Research specimens

- Ensure that participant has consented to have their blood drawn and stored for future research.

Collection Tube	8-10 cc mL clot activator Vacutainer tube (tiger top)
Label	Designated Barcode labels from Label Sheet
Processing	• Draw blood into participant labeled Vacutainer • Allow sample to clot for about 30 minutes at room temp. • Centrifuge at 1300g (2500 rpm) for 15 mins • Place a minimum of 0.5 mL of serum into each 1.4 mL Micronic vial • Sample to be divided between 6 x 1.4 mL Micronic vials • Store in -20 to -80° C freezer
Shipping	• Batch ship serum on dry ice (frozen) priority overnight to: Attn: Kendall Black Vermont Lung Center HSRF 227 149 Beaumont Avenue Burlington, VT 05405 Phone: 802 656 9984 Email: kendall.black@uvm.edu • Upon shipment, send email to University of Vermont and follow up for confirmation

5.4.2. Collecting blood for serum for storage/future use

Purpose

- To collect blood specimens for metabolic and oxidative markers and future studies

When

- V2 and V7

Draw blood:

- Prepare labels for all specimens collected.
 - Use labels from participant specific sheet of barcoded labels for aliquots. If spare labels are used, fill in with fine point, permanent marking pen. Print legibly. Refer to MOP Section 5.4.3 for detailed instructions on specimen labeling.
- Affix local participant labels to Vacutainers.
- Affix the appropriate barcoded specimen labels **lengthwise** to the **top** of 6 Micronic vials (1.4 mL) of serum.
- Collect at least 8 mL into 10 mL clot activator tube (tiger top).

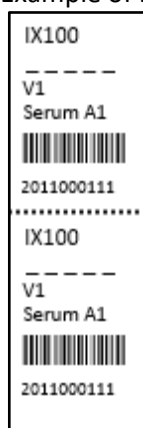
Serum (tiger top) processing:

- Allow sample to clot for about 30 minutes at room temperature.
- Centrifuge at 1300 g (2500 rpm) for 15 minutes.
- Transfer serum, using pipettes, (upper layer) into 6 labeled 1.4 mL screwtop Micronic vials. Do not transfer more than 1.0 mL into each vial.
- Cap the Micronic vials.
- Store Micronic vials in freezer between -20 to -80°C.

5.4.3. Biospecimen Labels for Micronic© vials

5.4.3.1. Overview

- Each sheet of labels has 36 labels that corresponds to one participant ID
- Specimen labels are printed in identical pairs: one for the specimen container (i.e., Micronic vial) and a matching one for the Specimen collection (BC) form
- Example of labels for participant IX100 at V1:



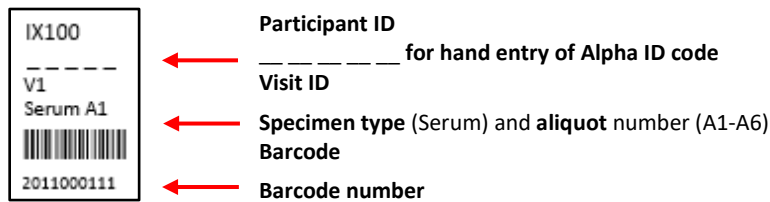
One of the labels for the matched pair for a specific specimen

The 2nd label for the matched pair

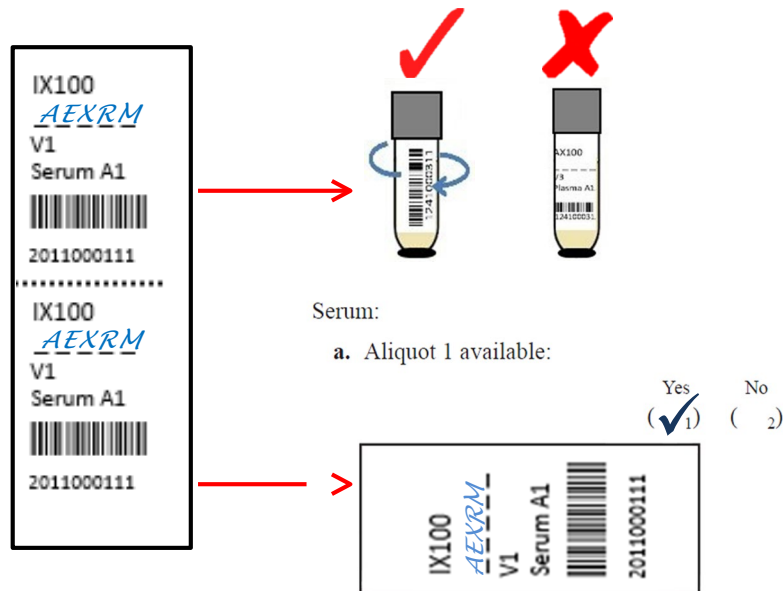
It is extremely important when you enroll a new participant that you make sure to use a participant ID for which you have a corresponding sheet of barcode labels. If labels are not available, notify the DCC immediately to acquire labels before enrollment.

5.4.3.2. Labels for specimens to be stored: the specifics

- Label diagram (one of a pair):

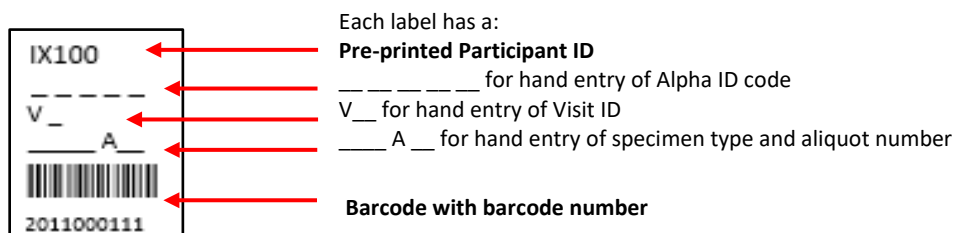


- Using the pre-printed barcode labels:
 - Fill in Alpha ID code on both labels
 - Attach 1st of the pair to the specimen container directly beneath the cap. Wrap the label around as shown for label to scan successfully
 - Cover label with clear scotch tape
 - Attach 2nd of the pair to the BC form in specimen-specific location



5.4.3.3. Spare labels

- Spare label diagram for each participant ID



It is extremely important to note that spare labels are to be used for the specific participant whose ID is pre-printed on it.

- Using the spare labels:
 - **Always use spare labels as a pair**
 - Use spare labels:
 - If the pre-printed labels are damaged or unusable
 - If pre-labeled were previously used (i.e., a failed collection at a prior)
 - If samples collected at a visit other than V2 or V7 (complete a UP form and indicate collection on BC form for that visit)
 - Fill in name code, visit ID, specimen type, and aliquot number
 - Attach 1 of the pair to specimen container and wrap clear tape around the label
 - Attach 2nd pair to the Specimen Collection (BC) form in appropriate box

5.4.4. Collecting and processing of specimens

5.4.4.1. Supplies for collection and processing

Supplied by DCC (only for biospecimens collected for future use)

- 1.4 mL Micronic vials for collection of serum
- Barcode Label Sheets for each TRIM study participant

Supplied by clinic

- Local participant labels for sample collection
- Needle (appropriate gauge for age of participant)
- Needle holder
- Gloves
- Swabs for cleaning blood draw site
- Band-Aids
- Scotch tape
- Emergency supplies readily available

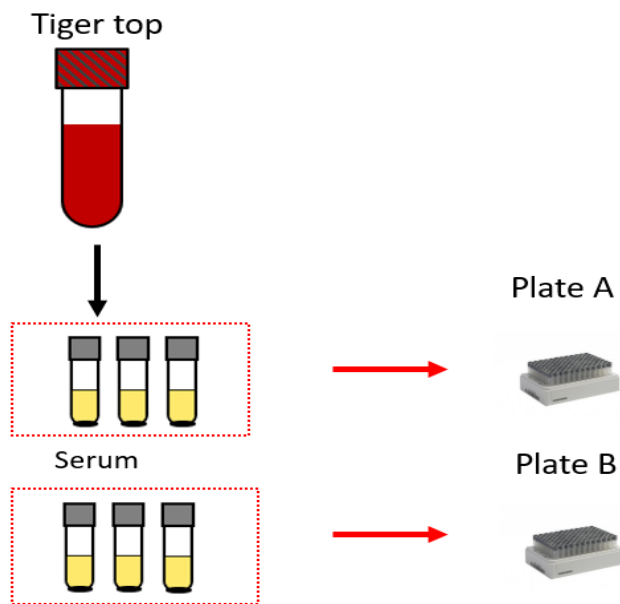
5.4.4.2. General requirements

- Gloves must be worn at all times when handling specimens. This includes during removal of the rubber stopper from the blood tubes, centrifugation, pipetting, disposal of contaminated tubes, and clean-up of any spills
- Tubes, needles, and pipettes must be properly disposed of in biohazard containers, in accordance with institutional requirements (<http://www.osha.gov/SLTC/biologicalagents/index.html>) should be followed, including gloves, eye protection or working in a biosafety cabinet for blood processing
- Use the appropriate barcode labels from the label sheet for each participant sample once processed

5.4.5. Specimen storage

Overview

- 96 well Micronic specimen trays should be filled on a continuous basis as participants proceed through the TRIM study.
- Specimens from each collection should be divided evenly between two 96 well Micronic plates, A and B (i.e., if 6 serum aliquots are collected at a participant's V2, 3 aliquots should go into plate A, and 3 into plate B). See image below for details.



5.4.6. Shipment of specimens for future use

When

- When two Micronic trays are full or at the end of the study

General overview

- Both A and B trays may be shipped when full or at the end of the study.
- An A and B tray set should NEVER be shipped on the same day.
- Log trays A and B in the TRIM data system to generate a shipping log.
- After entering clinical identification information, you will be prompted to enter the barcodes from each specimen into a web application.
- Scan each specimen vial with provided barcode reader and make sure the number entered on the screen matches the number printed beneath the barcode on the label.
- If your barcode scanner is malfunctioning or you are having difficulty scanning the barcodes, please make sure that:
 - There is no condensation over the label
 - Barcode scanner is plugged in and recognized by your computer. Individual labels that are difficult to scan may be entered by hand
 - If you believe your scanner is malfunctioning, contact the DCC to request a replacement
- Once all the barcodes for one shipment container are scanned, the system will generate a shipping log identifying all the specimens in your Micronic tray.
- Review log to make sure all specimens listed match those that are being shipped.
- Print a copy of the log to place in the shipment container, and retain another copy at the clinic.

Shipping supplies include

- Supplied by DCC
 - Styrofoam box with outer cardboard box (shipper)
 - Plastic biohazard specimen bag (8"X8')
 - Absorbent sheet
 - Dry ice label (UN1845)
 - UN3373 label
 - FedEx air bill
- Supplied by clinic
 - FedEx air bill
 - Packing material (bubble wrap, "peanuts", or crumpled newspaper)
 - Dry Ice

Planning your shipment

1. Be certain the lab will be available to receive specimens
 - a. Only ship Monday through Wednesday
 - b. Do not ship within 3 days of a holiday (labs may close for different holidays)
 - c. Assess that weather should not be a factor (no pending hurricane or snow storm) at your site, the receiving site or transfer (check FedEx for any warnings they may have posted)
2. Set aside sufficient time to complete the process; specimens are sensitive to changes in temperature; the process of scanning/packaging/shipping should not be interrupted

3. Have the following ready:
 - a. ALL specimens to be shipped
 - b. Shipping box/container with dry ice
 - c. Computer access to TRIM site, printer, and barcode scanner
4. Shipments are to be done by TRIM coordinator who is:
 - a. Familiar with the TRIM specimen shipment protocol
 - b. IATA certified

Note: If specimens are to be packed and/or shipped by a non-TRIM staff member, it is the responsibility of the Lead Coordinator to train and verify the shipment is performed per TRIM requirements.

5. Remember the limit is one shipment per day.

General packing and shipping tasks

Specimen plates should be shipped every six months or when full. A and B specimen plates should NEVER be shipped on the same day, to avoid the possibility of loss.

5.4.7. How to scan study specimens and prepare the Specimen Shipment Record

1. Go to the appropriate study website and select specimen shipping. Accessing the shipping page will require you to log in.

ACRC Login

Clinic:	<no selection>
PIN:	
Password:	
	Login Reset

Note: Currently the data entry page is viewable only in Internet Explorer version 9 and below. If you are using Internet Explorer 10 or higher, please enable Compatibility View and add "jhcct.org" to the list of websites to be displayed in that mode.

2. Click on "Specimen Shipping and Receipt"
3. On the following screen, click on "Ship Specimens". The screen for Specimen processing and tracing includes:
 - a. Simple instructions (at top of page)
 - b. Display of barcode(s) scanned for shipment as entered
 - c. A brief description of any specimen with issues, such as "specimen not found"
 - i. **Note: The system will know to expect a sample barcode only if the BC form is entered into the data system.**
4. With the cursor placed in the box next to "Scan specimen here", scan the barcode on the sample to be shipped
 - a. Verify that sample has been added to list of specimens for shipment
 - b. Confirm that the participant ID and visit ID correspond to the label on the specimen
 - c. Systematically scan all specimens for shipment
 - i. Keep the specimens at the appropriate temperature before and immediately after scanning specimens
 - ii. If there are errors or issues with scanning a specimen, please refer to **Table 2**.

Tips and other important information

- Only scan one vial at a time. The laser used to scan the barcode is quite long, so attempting to scan vials in close proximity to each other may result in recoding an incorrect barcode.
- If a barcode is unable to be scanned, it can also be typed in.

For other issues refer to Troubleshooting below or contact the DCC at JHSPH.ala-acrc@jhu.edu

5. Verify the total number of specimens scanned equals the number being shipped
6. Click the “Done scanning, Continue” button
7. Click “OK” when prompted to “Save data and prepare shipment log”
8. Print out the Specimen Shipping Log that is displayed on the following page
 - a. Click “Print” button
 - i. **Note: If you are unable to print to a printer at the moment, you can print to PDF (providing you have Adobe Acrobat installed on your computer).**
 - b. Print two copies of the Specimen Shipping Log
 - i. One copy to be included as the shipping record
 - ii. Additional copy to store for your records

5.4.8. General packaging and shipping procedures

1. Shipments are to be done by ACRC staff member who is:
 - a. Familiar with shipping specimens
 - b. IATA certified
2. Prepare shipper box:
 - a. Fill Styrofoam shipper halfway with dry ice
 - i. Styrofoam shipper box is to be filled with **at least 10 pounds** of dry ice
 - b. Affix proper labels on outside of cardboard shipper box
 - i. UN3373 label (Biological Specimens)
 - ii. UN1845 label (Dry ice label)
3. Specimens should remain frozen throughout the packaging and shipping process
4. Ensure the lid on the 96 well plate is securely fastened. Place plate into a separate clear Biohazard bag and seal.
5. Place the overwrapped 96 well plate in the Styrofoam shipper
6. Cover plate with the remaining dry ice
 - a. There should be little room for air in the container. Extra moisture resistant packing material can be used to fill the container or eliminate more air space
7. Place Styrofoam cover on the container
8. Place signed shipping record (print out of scanned specimens) in a sealed bag on top (outside) of the Styrofoam lid
9. Seal cardboard shipper with packing tape
10. Prepare FedEx airbill:
 - a. TRIM FedEx account to charge is 970808213
 - b. Item 4a: Express Package Service check FedEx Priority Overnight
 - c. Item 5: Packaging – select other
 - d. Item 6: Special Handling
 - i. Indicate “Yes. Shipper’s Declaration not required”
 - ii. Check “Dry Ice” and fill in weight of dry ice in kilograms (10 lbs. = 4.4 kg)
 - e. Verify that Biological Specimen and Dry Ice labels are attached to shipper

- f. Item 3: Recipient to ship to:
 - Attn: Kendall Black
 - Vermont Lung Center
 - HSRF 227
 - 149 Beaumont Avenue
 - Burlington, VT 05405
 - Phone: (802) 656-9984
- g. Affix FedEx label to shipper
- h. Verify shipment is for same day pick up
- 11. Immediately upon shipment, notify lab by sending email to kendall.black@uvm.edu. Include FedEx tracking number in email
- 12. Shipment is not considered complete until you have verified that it arrived at the lab by:
 - a. Email from lab or
 - b. FedEx confirmation (with tracking number)

Tracking specimen shipments with FedEx

- To track a shipment on FedEx.com, click the following link:
https://www.fedex.com/apps/fedextrack/?action=track&cntry_code=us

Troubleshooting for specimen shipments (biospecimens for future use only)

The table below includes suggestions for solving and preventing problems with specimen shipment. If you have an issue that is not addressed below, you can submit a data feedback form or call the DCC. Since the system will not save information if it times out, you may find it preferable not to ship a “problem” specimen with a later shipment.

- **Note: At this time, specimens without barcodes and specimens with barcodes that cannot be read (i.e., rubbed off in part or in full) cannot be shipped, but should be kept in appropriate storage conditions until system can accommodate them.**

Table 2

Issue	Solution (s)	Prevention
Scans (can see the light, hear the beep) but number does not show up on screen	1. Be certain cursor is in the box for the value to go in. 2. Be sure that scanner is securely attached to the computer. 3. Barcode number can be typed in if scanner not working.	
Specimen has a spare label on it	Scan the same as for other barcode labels. Spare label is participant and specimen specific.	Before using labels always verify: Right participant Right specimen Right visit
The label is for the correct participant , but the wrong specimen type	1. Complete a spare label for the correct participant and specimen type 2. Dry off tube. 3. Apply new label and apply clear tape over label 4. Attach 2nd spare label to the BC form 5. Amend data entry of BC form with new barcode; include notation regarding event 6. Notify DCC	Always verify: Right participant Right specimen Right visit Right place (one on specimen one on BC form)
The label is for the wrong participant, but with 100% certainty the correct participant ID is known	Re-label with extreme care: 1. Complete the correct label (if available) or complete spare labels 2. Dry outside of tube or cryovial 3. Apply new label and apply clear tape over label 4. Attach matched 2nd label to the BC form 5. Amend data entry of BC form with new barcode 6. Complete a UP form and notify the DCC	Always verify: Right participant Right specimen Right visit Right place (one on specimen one on BC form)

Issue	Solution (s)	Prevention
System gives message that specimen has not been collected. If it is because: 1. BC form not data entered 2. BC barcode entry does not match barcode on specimen tube 3. Barcode not in system because specimen labels applied incorrectly (applied duplicate labels to specimens and BC resulting in specimens having one set of matched labels and the BC having the other matched set)	Message indicates only that barcode data from BC is not in the system. Solutions: 1. Verify whether the BC form has not been entered. Manually verify that barcode labels match and ship. 2. Compare specimen label to BC form label. Remember the specimen ID must be identical before specimen can be shipped. Correct BC entry if necessary. Note: This is more likely to happen if barcode information is typed in. 3. Requires re-labeling: - Carefully complete spare label sets - Dry outside of tube or cryovial - Apply new label(s) and apply clear tape over the label on specimen(s) - Attach matched 2nd label(s) to the BC form - Amend data entry of BC form with new barcode information - Complete a UP form	- Enter BC data within 10 days of visit and - Use barcode scanner to enter barcode in data system - Always verify labels are applied one to specimen and one to BC form
How do I know what specimens I need to ship	Access the Specimen Status page to see status of all specimens	
Will the data system save a partially entered shipment	If the page times out, the data entered will be lost. <i>Note: Page times out after about 15 minutes.</i>	Set aside enough time to scan, package and ship specimens as one continuous process.
What if I can't print the shipping log/manifest	If the page cannot be printed to paper, the following are suggested: 1. Print to PDF and save to your computer 2. Use print screen function and save as a file Remember this log is for your records and is to be included in the shipping container. Do not ship specimens without it.	Always have printer access when entering shipment.

5.5. Questionnaire administration

5.5.1. Questionnaires

Purpose

To collect information directly from the participant concerning aspects of participant's asthma

Summary

- Asthma Control Test (ACT)
- Asthma Symptom Utility Index (ASUI)
- Gastrointestinal Symptom Rating Scale (GSRS)
- Marks Asthma Quality of Life Questionnaire (MAQL)
- Patient Health Questionnaire (PHQ-9/GAD-7)
- Quality of Life by RAND Health (SF-36V1)
- Suicide Screening Worksheet (SSW)

Timeframe*

- Asthma Control Test (ACT) is used to collect data on asthma symptoms over the last 4 weeks
- The Asthma Symptom Utility Index (ASUI) is used to collect data on the frequency and severity of asthma symptoms over the past 2 weeks
- Gastrointestinal Symptom Rating Scale (GSRS) is used to assess gastrointestinal symptoms over the last week
- Marks Asthma Quality of Life Questionnaire (MAQL) is used to collect data about how asthma affects the participant's quality of life
- Patient Health Questionnaire (PHQ-9/GAD-7) is used to collect data about the participant's anxiety and depression over the last 2 weeks
- Quality of Life by RAND Health (SF-36V1) is used to collect data on how the participant views their overall health
- Suicide Screening Worksheet (SSW) is used to assess suicide risk

* Please refer to individual questionnaires for specific instructions on administration, completion, and scoring.

5.5.2. General administration guidelines

General administration guidelines

- Administer all tests according to the directions on the forms. Some questionnaires are handed to the participant to complete. Others are read to the participant.
 - Participant completes: Asthma Control Test (ACT), Gastrointestinal Symptom Rating Scale (GSRS), Marks Asthma Quality of Life Questionnaire (MAQL), Patient Health Questionnaire (PHQ-9/GAD-7), Quality of Life by RAND Health (SF-36 V1)
 - Questionnaires read to participant: Asthma Symptom Utility Index (ASUI), Suicide Screening Worksheet (SSW)
- If questions are read
 - Do not rephrase items unless instructions specify that this is allowed.
 - Speak loudly and clearly.
 - Read all instructions as written. Summarize and give further explanation as needed.

- Make accommodations for auditory or other deficits. In case of hearing impairments, be sure to look at the participant when speaking, speak in lower tones, and do not speak too quickly.

Rapport

Establishing rapport with a participant or caregiver is important to elicit cooperation with study procedures. The interaction between the coordinator and participant could affect the participant's performance and responses. Answering questions about mental health issues may be threatening to some people. Establishing rapport is essential so that participants are at ease and comfortable. A participant who is anxious or uncomfortable will be too distracted to answer questions.

Try to establish rapport and put the participant and/or caregiver at ease before beginning. Engage in casual conversation before administering the assessments. Some additional tips are below:

- Always be pleasant and patient.
- Check to make sure the participant is comfortable (e.g., warm enough, need to use restroom, etc.).
- Be sure to give them a good idea of exactly what will happen during the visit before beginning.
- Do not rush any of the aspects of your interaction with the participant or caregiver.
- Allow them sufficient time to respond and to ask questions.
- Keep in mind that each person's personality will be different and some will respond better to you than others. Adjust your interaction with them accordingly.
- Always thank the participant at the end of the session. Say something like, "I want to thank you for your participation today. I really appreciate your effort, attention, and time. It was a pleasure working with you."

Creating an appropriate environment

It is important to create an appropriate environment for the administration of the assessments so that the participants and caregivers feel comfortable and can focus on answering the questions accurately. Some additional tips for achieving this are below:

- Ahead of time, ensure that the participant and caregiver understand how long the visit will last.
- Ahead of time, ensure that participants and caregivers bring all necessary eyewear and/or hearing aids with them to the visit.
- Prepare all materials for the visit ahead of time (although the data collection forms should be printed just prior to the visit to ensure that all the forms are up-to-date).
- Ensure there is a plan for appropriate restroom breaks, meals/snacks, personnel to accompany participants while in the waiting room, if applicable
- The room should be private and quiet.
- The room should be free of distractions with proper lighting and temperature regulation, comfortable seating, and adequate working space for the participant.
- Silence any mobile phones (administrators and participants).
- Prevent interruptions by placing a "Quiet Please. Study visit in progress" sign on the door.
- Be prepared with all of the materials you will need and put them within easy reach. This will minimize fumbling, paper shuffling, and searching.
- Keep the surface uncluttered and free of excess materials.

Copyrights

- Several of the tests used have been obtained and/or purchased through copyright agreements with the authors and publisher. Assessments can only be used for this study and should not be used for any other purpose.

5.5.3. Gastrointestinal Symptom Rating Scale (GSRS)

Purpose

- To assess gastrointestinal symptoms
- The questionnaire asks participants about their gastrointestinal symptoms **during the week prior** to a clinic visit.

When

- V1-V7, all visits

Who

- Participant completes the GSRS questionnaire

Instructions

- Coordinator hands GSRS to participant to complete
- Make sure participants complete the entirety of the questionnaire **before** leaving the clinic
- Key into the TRIM data system within **10 working days**.
- If score on any item is ≥ 6 , discuss the item with the study PI and/or study physician immediately. This indicates a symptom of severe or very severe discomfort and should be addressed as soon as possible.
 - This is considered an adverse event. An Unanticipated Problem (UP) form should be filled out and reported to the DCC within 5 calendar days.

5.5.4. Patient Health Questionnaire for Depression and Anxiety (PHQ-9 & GAD-7)

Purpose

- Patient Health Questionnaire is a diagnostic tool for mental health disorders used by health care professionals that is quick and easy for patients to complete.
- PHQ-9 and GAD-7 are used to determine eligibility at V1
- To monitor for safety V2 to V7 since the side effect of roflumilast is suicidality and increased depression and anxiety.

Form

- Patient Health Questionnaire (PHQ-9 and GAD-7) (HQ) form

When

- V1 to V7, every visit

Instructions

- Clinic coordinator hands the HQ form to the participant to complete.
- The clinic coordinator reviews participant responses after administering:
 - Check for missing responses and resolve any problems before the participant leaves the clinic.

- Calculate total scores for PHQ-9 and GAD-7 before the end of visit.
- If the answer on item 9 is greater than 0, complete the Suicidal Severity Screener Worksheet (SSW) to assess risk. See Suicidality Severity Screener section.
- At the V1 or V2 visit, before randomization
 - If the total PHQ-9 score (item 10) is 15 or more and the total GAD-7 score (item 19) is 10 or more points, participant should not be enrolled or randomized
 - See section 5.5.5. for instructions.
- At V3-V7
 - If the total PHQ-9 score (item 10) is 15 or more and the total GAD-7 score (item 19) is 10 or more points OR
 - If there is a change in score totaling 5 or more, from baseline (V2)
 - It is an adverse event, and, as such, followed until resolution or a plan for care under the supervision of another medical provider is established.
 - The Suicide Screening Worksheet (SSW) should be filled out along with an Unanticipated Problem (UP) form or a Serious Adverse Event (SR) form depending on the severity of the score change
 - If the participant has thoughts of suicide or hurting him/herself, inform the Director and follow-up with the participant according to local clinic guidelines for potential suicidality.
 - See section 5.5.5.
- Item 11 after scoring (the single potential participant's-rated difficulty item), is not used in calculating score but rather represents the potential participant's global impression of symptom-related impairment.

Scoring guidelines

- Calculate total scores for PHQ-9 and GAD-7 before end of visit by adding up individual items.
- There are 9 items in the PHQ-9, each of which is scored 0 to 3, providing a 0 to 27 severity score.
- There are 7 items in the GAD-7, each of which is scored 0 to 3, providing a 0 to 21 severity score.
- Scores must be ≤ 9 for study enrollment and to continue in study.
- If scores increase by ≥ 5 compared with V2, participant cannot continue in study

Interpretation

- Higher scores indicate more depressive symptoms. Typically, scores of greater than or equal to 5, 10, and 15 represent mild, moderate, and severe levels of depressive symptoms.

Reference

Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001 Sep; 16(9): 606-13.

5.5.5. Handling elevated symptoms: Depression, anxiety, and self-harm

The questionnaires used include questions regarding the participant's health- both physical and mental. If a participant is experiencing a mental health crisis, sites must be prepared to provide them with additional support and referrals as needed. All participating sites must identify a psychologist or licensed psychologist to be used a resource for your site, and create and maintain mental health resource information to offer to participants who present with symptoms of major depression, anxiety, or suicidality.

Mental health resource information should contain the following:

- Crisis numbers, including:
 - The National Strategy for Suicide Prevention, 1-800-273-TALK (8255). A free, 24-hour hotline available to anyone in suicidal crisis or emotional distress; your call will be routed to the nearest crisis center to you.
 - Local or state crisis numbers
- Three or more local psychiatry practices, at least one of which is for low-income patients

This list should be submitted to your IRB at start-up. Sites should maintain multiple copies of their mental health resource information in the clinic so the list can be distributed to participants as needed.

Protocol for participant with elevated depression and anxiety symptoms

The PHQ-9/ GAD-7 (HQ form) captures the presence and severity of depression and anxiety symptoms. Scores above the specified thresholds suggests a clinically significant level of psychological distress. It does not necessarily mean that the participant has a clinical diagnosis of depression or anxiety but clinics need to ensure they are receiving appropriate care.

- **Elevated depression scores**

Elevated depression scores are defined as: Total score of 15 or greater on the depression questions of the PHQ-9 (HQ form). If depression scores are elevated, say:

 - *"It seems that you are "down" or somewhat distressed. I would like to give you a few names and numbers of people in the community you can contact for assistance."* OR *"Your score is a bit high. Are you feeling "down" or upset? Would you like to have some names and numbers to contact for help?"*
 - Offer patient the mental health resource information
 - Follow up with participants who have elevated depression by phone within 7 days to check on follow up with mental health care resources, or mail them a letter with resources if we are unable to reach them by phone.

- **Elevated anxiety scores**

Elevated anxiety scores are defined as: Total score of 10 or greater on the anxiety questions of the GAD-7 (HQ form). If anxiety scores are elevated, say:

- *"It seems that your anxiety may be causing you a lot of stress. I would like to give you a few names and numbers of people in the community you can contact for assistance."* OR *"Your score is a bit high. Are you feeling anxious or 'on edge' a lot? Would you like to have some names and numbers to contact for help?"*
 - Offer patient the mental health resource information
 - Follow up with participants who have elevated anxiety by phone within 7 days to check on follow up with mental health care resources, or mail them a letter with resources if we are unable to reach them by phone.
- **Note:** If the participant has elevated scores, refer them to get further evaluation and treatment, document the referral to the patient and their primary care physician/mental health provider, and document the event as an unanticipated problem on a UP form.

Significant changes in depression and anxiety scores

- Subsequent scores exceeding the threshold score, or the minimally clinically important difference for the questionnaires when compared to Visit 2 (greater or equal to 5) will be considered an adverse event, and, as such, followed until resolution or a plan for care under the supervision of another medical provider is established.
- Check PHQ-9 and GAD-7 scores from the last visit and compare with the current scores
- If the scores increase ≥ 5 compared with V2, this will be considered an adverse event
- Document on the Patient Health Questionnaire (HQ) form in the HQ Worksheet section
- Follow until resolution or a plan for care under the supervision of another medical provider is established.
- Make arrangements with the participant to return all study drug back to the clinic, if participant has been randomized and given study drug

Protocol for participants exhibiting potential for self-harm

If a participant discloses that they may do harm to themselves, we must follow up with the participant and report to PI. Please follow the procedures listed below if a participant:

- Answers with a score of greater than 0 on Question 9 on the PHQ-9 (HQ form)
- Administer Suicidality Severity Screener (SSW form, available as worksheet on study website); this worksheet was adapted from the Columbia-Suicide Severity Rating Scale (C-SSRS), by Posner, K., et al.
- Assess risk and proceed as per directions on the SSW form.

Suicidal Severity Screener procedures:

- Start by saying “You mentioned on some of the questions that you have thoughts about killing yourself. Tell me about those thoughts.”
- Ask all questions as written. See questions below.
- Review the completed questionnaire for missing responses.
- Follow up with participant and study physician per risk assessment.
- Keep a copy of this worksheet in the participant’s study file.

7. Have you been thinking about how you might kill yourself:
8. Have you had these thoughts and had some intention of acting on them:
9. Have you started to work out or worked out the details of how to kill yourself:
10. Do you intend to carry out any plans you have:
11. Do you have a current mental health provider? If “Yes,” when is your next appointment:

If participant answers “No” to items 7, 8, 9, and 10, they are classified as Mild Risk. Staff must:

- Notify PI
- Provide resource guide, including suicide hotline number, with statement: *“It sounds like you currently have some thoughts about suicide but do not plan to go through with it. If you notice the thoughts become more frequent, or you want to talk with someone, please call this number.”*
- If they have a provider, make sure there is an upcoming appointment scheduled to talk about their concerns. If they do not have a provider, indicate possible providers on resource sheet.
- Complete an Unanticipated Problem (UP) form documenting the outcome of this questionnaire and subsequent action taken.

If participant answers “Yes” to items 7 or 8, but NOT to items 9 or 10, they are classified as Moderate Risk. Staff must:

- Notify PI
- Provide resource guide, including suicide hotline number, with statement: *“It sounds like you currently have some thoughts about suicide but do not plan to go through with it. If you notice the thoughts become more frequent, or you want to talk with someone, please call this number.”*
- If they have a provider, make sure there is an upcoming appointment scheduled to talk about their concerns. If they do not have a provider, staff should strongly encourage them to contact the suicide hotline and/or one of the local providers listed to schedule a follow up call or appointment.
Staff should encourage participants to contact the hotline or schedule an appointment before concluding the study visit.
- Complete an Unanticipated Problem (UP) form documenting the outcome of this questionnaire and subsequent action taken.
- Contact the participant by phone two weeks after visit to confirm they are receiving follow up care. Update UP form with results of phone call.

If participant answers “Yes” to items 9 or 10, they are classified as Immediate Risk. Staff must:

- Notify PI
- Instruct them to call PCP, 911, or appropriate crisis number and give participant resource guide highlighting 24-hour help lines. If participant does not call for assistance, let them know you are obligated to report this to emergency services; walk participant to ER or call 911.
- If concerned there is an immediate risk, walk the participant to the ER or call 911.
- Complete a Serious Adverse Event Report (SR) form documenting the outcome of this questionnaire and subsequent action taken.
- Contact the participant by phone two weeks after visit to confirm they are receiving follow up care. Update SR form with results of phone call.

5.6. Peak flow measures

Purpose

- Measure peak flow to determine change in morning peak expiratory flow rate (PEFR) as a study outcome and as a method of self-monitoring for participants

When

- Daily throughout the study
- Morning peak flow at least 6 hours after last dose of asthma medications and before morning dose of asthma medications
- At V1 to calculate Asthma Action Plan (AAP) Card zones
 - **Note: Disposable one-way valve mouthpieces can be used for peak flow at V1**

Equipment

- Mini-Wright Peak Flow Meter

Testing procedure

- Instruct participant to:
 - Stand up and relax. Always measure peak flow in the same position
 - Slide the red indicator to zero and insert the mouthpiece. Be sure your fingers do not obstruct the slot in where the pointer slides or the end where the air comes out. Be sure to point the meter straight out, parallel to the ground
 - Take a deep breath
 - While holding breath, place the Peak Flow Meter in mouth- on tongue – then close lips around the mouthpiece
 - Blow out as hard and as fast as possible. One second is long enough to blow out. Do not puff air out with cheeks, use lungs to force the air out
- Write down the number read off the meter
- Repeat measurements 2 to 5 more times. The goal is to match the two highest blows within 40 LMP; that is, the two highest numbers should be within 40 and above or below each other
- Reset indicator to zero before you repeat the measurement
- Report the highest number measured on the appropriate form
- Participant records daily in Asthma Diary
- At V1, record participants three efforts on the Screening (SC) form and the personal best on the Asthma Action Plan (AAP) Card
 - **Note: Personal best for AAP Card is the highest peak flow of three efforts from V1**

Forms (abbreviation)

- Screening (SC) form

Information sheets (abbreviation)

- Asthma Action Plan (AAP) Card*
 - Instructions for Measuring Peak Flow (IPF)*
- *Not entered into data system

5.7. TRIM Asthma Action Plan (AAP)

Purpose

- To outline, for participant, how to respond to asthma symptoms

When

- At all study visits, participants will be counseled to follow the guidelines on his/her TRIM AAP Card and will be told to seek medical attention at an urgent care facility for emergencies.

Tasks

- At screening visit (V1)
 - Fill in “personal best” peak flow on AAP Card. “Personal best” for AAP is the highest of the three peak flow readings done at V1. Values should be recorded on the Screening (SC) form.
 - Fill in green, yellow, and red zone cut-off values on AAP Card. Cut-off values may be hand calculated using the following:
 - Green zone: > **0.80** of personal best
 - Yellow zone: **0.50 to 0.79** of personal best
 - Red zone: < **0.50** of personal best
 - Fill in contact information
 - AAP values are also to be recorded on the SC form
 - Review instructions for use of card
 - Values for the AAP Card should also be recorded on the Screening (SC) form
 - At all other study visits (V2-V7), review TRIM AAP Card

5.8. TRIM Diary Cards

Purpose

- To record asthma symptoms on a daily basis

When

- Participant should complete an asthma Diary Card entry on a daily basis from date on enrollment. They should bring their completed asthma diaries to each clinic visit.

Tasks

- At screening visit (V1)
 - Distribute asthma Diary Card packets (in participant folder)
 - Supply sufficient asthma Diary Card packets to cover time to next visit
 - Pre-print asthma Diary Card packets with days, dates, and participant ID by clicking on the appropriate link of the data system menu of TRIM homepage
 - Spare Asthma Diary- include one packet not prefilled with days and dates
 - Review Instructions for TRIM Diary Card with the participant (IDC)
 - To complete an asthma diary card entry each morning
 - If a day is missed, they are to skip that page and fill in the page for the next day. Remind participant that pages are marked with day and date.
 - If a response needs to be changed, draw a line through the mistake and circle correct response
- At V2-V7
 - Collect TRIM Diary (DC) Card packets distributed at prior visit
 - Review TRIM diary Card entries with participant (DCs should be both legible and complete)
 - At V2-V6 Distribute asthma Diary Card packets and review instructions with the participant
 - Distribute asthma Diary Card packets with preprinted dates and one spare packet

Forms (abbreviation)

- TRIM Diary (DC) Cards

Information sheets (abbreviation)

- Instructions for TRIM Diary Card (IDC)*
*Not entered into data system

6. Event reporting: SAEs and unanticipated problems

6.1. Definitions

Adverse event*: Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with a person's participation in the research, whether or not considered related to a person's participation in the research.

Serious adverse event (SAE)*: Any Adverse Event that meets any of the following criteria:

1. Results in death
2. Is life-threatening (i.e., places a participant at immediate risk of death from the event as it occurred)
3. Requires inpatient hospitalization or prolongation of existing hospitalization
4. Results in a persistent or significant disability/incapacity
5. Results in a congenital anomaly/birth defect
6. Any other adverse event that, based upon appropriate medical judgement, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (i.e., allergic bronchospasm requiring intensive treatment in the emergency room or at home).

Relatedness: ** Relatedness refers to the extent to which an adverse event is considered to be related to the intervention or study procedures. An adverse event is considered related if there is a reasonable possibility that the event may have been caused by the procedure. In the TRIM study, the relatedness of an event can only be determined by the primary investigator.

The following definitions apply to relatedness:

- **Unrelated**
 - Adverse event is clearly due to extraneous causes (i.e., underlying disease, environment)
- **Unlikely** (Adverse event **must meet 2** of the following):
 - Does not have temporal relationship to intervention
 - Could readily have been produced by the participant's clinical state
 - Could have been due to environmental or other interventions
 - Does not follow known pattern of response to intervention
 - Does not reappear or worsen with reintroduction of intervention
- **Possible** (Adverse event **must meet 2** of the following):
 - Has a reasonable temporal relationship to intervention
 - Could not readily have been produced by the participant's clinical state
 - Could not readily have been due to environmental or other interventions
 - Follows a known pattern of response to intervention
- **Probable** (Adverse event **must meet 3** of the following):
 - Has a reasonable temporal relationship to intervention
 - Could not readily have been produced by the participant's clinical state or have been due to environmental or other interventions
 - Follows a known pattern of response to intervention
 - Disappears or decreases with reduction in dose or cessation of intervention

- **Definite** (Adverse event **must meet 4** of the following):
 - Has a reasonable temporal relationship to intervention
 - Could not readily have been produced by the participant's clinical state or have been due to environmental or other interventions
 - Follows a known pattern of response to intervention
 - Disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure

Expectedness: An unexpected event is one that has not been documented previously as an established adverse reaction to the study intervention and that is not recognized as part of the natural progression of the disease.

A particular event may also be considered unexpected if it has a higher severity grade than what has been documented or identified previously. Events that occur as a consequence of study procedures and are not noted in the informed consent document are also considered unexpected in nature.

Unanticipated problem (UP)*: Any incident, experience, or outcome that meets all of the following criteria:

1. Unexpected in terms of nature, severity, or frequency, taking protocol research procedures and participation population characteristics into consideration
2. Related or possibly related to a persons' participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
3. Places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

Examples of unanticipated problems may include:

1. Unusual medical events: medical events that are not considered "serious" but may be important for the study, such as a reaction to a study procedure such as spirometry, pregnancy, a suspected safety issue concerning any aspect of the trial
2. Atypical problems: examples of these include breach of confidentiality and inadvertent loss of study records
3. Communications that need to be recorded but are not captured on other data forms

Expected adverse events that are more frequent or severe than expected may become Unanticipated Problems

Protocol deviation*: Any change, divergence, or departure from the IRB-approved research protocol. The impact of a Protocol Deviation is characterized by designation as serious or not serious.

Examples of not serious Protocol Deviations include, but are not limited to:

1. Scheduling a protocol visit slightly outside of the timing in the protocol, but at a time that would not compromise the interpretation of the study data or impact the health of the participant
2. Inability to obtain a sample that is needed for exploratory analysis that does not impact the health of the participant
3. Protocol specifications for clinical testing are not followed

Examples of serious Protocol Deviations

1. The deviation has harmed or posed a significant or substantive risk of harm to the research participant. Examples include, but are not limited to: a research participant received the wrong treatment or incorrect dose or a research participant received an excluded concomitant medication.
2. The deviation compromised the scientific integrity of the data collected for the study. Examples include, but are not limited to: a research participant was enrolled but does not meet the protocol's eligibility criteria or changing the protocol without prior IRB approval
3. The deviation is a breach of human participant protection regulations or NIH policies or procedures. Examples include, but are not limited to: failure to obtain informed consent prior to initiation or study-related procedures, performing tests or procedures beyond those anticipated in the protocol or by those not approved to perform such actions by the IRB, or falsifying research or medical records
4. The deviation involves a serious or continuing noncompliance with applicable federal, state, local or institutional human participant protection laws, regulations, or policies, or procedures. Examples include, but are not limited to: working under an expired professional license or certification, failure to follow federal and/or local regulations, and intermural research or NIH Clinical Center policies, or repeated protocol deviations (i.e., a study site repeatedly performing a study assessment incorrectly despite recognition of the problem)
5. The deviation is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles. Examples include, but are not limited to: a breach of confidentiality and/or privacy, or inadequate or improper informed consent procedures

Some serious protocol deviations may place the participant at a greater risk of physical or psychological harm. In such cases, the event should be reported on the Unanticipated Problem (UP) form.

Noncompliance*: The failure to comply with applicable NIH HRPP policies, IRB requirements, or regulatory requirements for the protection of human research participants. There are three types of non-compliance:

1. Serious non-compliance: Non-compliance that: increases risks, or causes harm to participants, decreases potential benefits to participants, compromises the integrity of the NIH HRPP, or invalidates the study data
2. Continuing non-compliance: Non-compliance that is recurring. It could also include a failure to respond to IRB requests to resolve previous allegations of non-compliance
3. Minor (non-serious) non-compliance: Non-compliance that is neither serious nor continuing.

*NIH HRPP SOP 16 v2 (10/1/13), Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations

† National Institutes of Health, Office of Human Subjects Research, Adverse Event Reports, May 26, 2000, Appendix 2

‡ US Department of Health and Human Services, Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 15, 2007

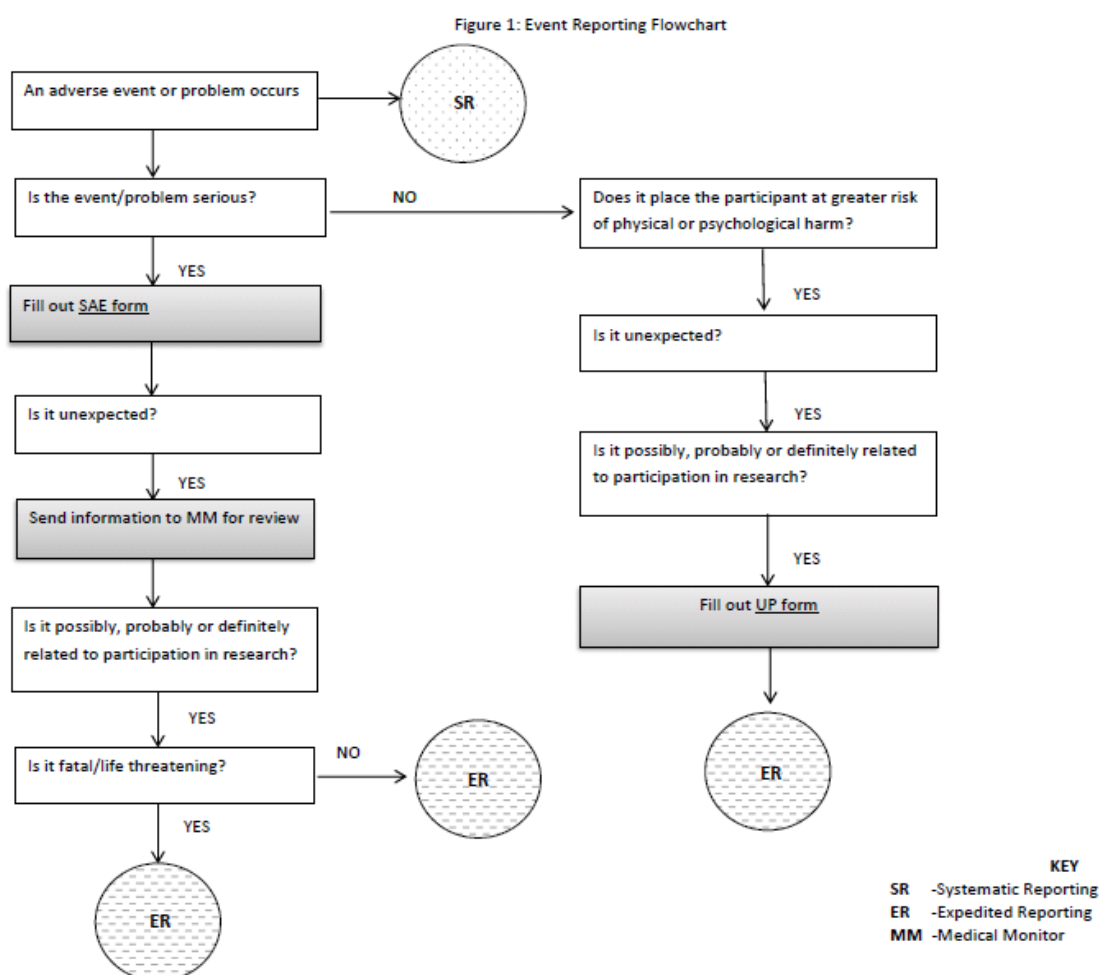
6.2. Event reporting

Adverse events may occur over the course of a study. Site personnel are responsible for documenting all adverse events and problems in the study database regardless of severity or other characteristics.

Some adverse events and problems require expedited reporting to regulatory agencies. Site PIs are required to promptly report all serious adverse events (SAEs) and unanticipated problems to the study DCC, including an assessment of relatedness and expectedness.

Dr. Robert Wise in the Medical Monitor (MM) for TRIM, and he is responsible for the review of serious and unexpected adverse events across the study. The DCC must send all unexpected SAEs to the study MM for final assessment of relatedness and expectedness. The MM may provide feedback on prognosis and treatment. In all cases, the MM's assessment determines the reporting requirements.

Figure 1 describes the process site PIs should follow in classifying adverse events and determining the action required. Events in this figure are labeled as those that require Systematic Reporting (SR) and those that also require Expedited Reporting (ER).



6.3. Serious adverse events reporting

Purpose

- To report an occurrence of a serious adverse event (SAE)

Events to be reported

- Any serious adverse event that meets the definition of serious adverse event in section 6.1 above

By whom

- Identification of a serious adverse event is the responsibility of the Study Physician

When

- As needed whenever a serious unexpected adverse event associated with study treatment or study procedures is first reported or whenever a follow-up information is received
- Must report to the DCC within 3 calendar days of becoming aware of the SAE

To Whom

- DCC
- IRB per institution's IRB guidelines

Tasks

- Report a serious adverse event to the DCC within 5 calendar days of learning of the event
- To report, key the Serious Adverse Event Report (SR) form at www.cctrials.org/alaacrc; include as much information as possible. Key within 5 calendar days even if some data is missing.
- Email the DCC if receipt of this report is not confirmed within 3 calendar days. Email JHSPH.alaacrc@jhu.edu; indicate Serious Adverse Event in subject line and indicate high priority.
- Submit new information and/or follow-up information by editing the form including resolution of event. Follow-up information to be added when:
 - The serious adverse event is resolved
 - There is a significant change in the patient's condition
 - The physician's judgement regarding the event has changed
- The Study Physician should use his/her judgement in deciding what is significant
- Record event on CV form, in the Interim Medical History section

Forms (abbreviation)

- Clinic Visit (CV)
- Serious Adverse Event Report (SR)

6.4. Unanticipated problem: definition and reporting

Purpose

- To report an occurrence of an unanticipated event or problem

Events to be reported

Two categories of unanticipated problems are not to be reported:

- Unusual events:
 - Unusual medical events- medical events that are not Serious Adverse Events but a PI or coordinator feel should be brought to the attention of the medical officer at the DCC. These can include:
 - Medical events that are not considered “serious” but may be important for the study
 - Examples: a suspected safety issue concerning any aspect of the trial
 - Atypical problems:
 - Examples: destruction of study records
 - Communications that need to be recorded but are not captured on other data forms
- Protocol deviations that are serious (i.e., involve increased risk) are reported as unanticipated problems in an expedited manner. Protocol deviations should be reported on the UP form, if they meet the following criteria:
 - The protocol deviation increases the chance of risk for the participant
 - The protocol deviation is unexpected
 - The protocol deviation is related to the research

When

- As needed, whenever an unanticipated problem is first reported or whenever follow-up information is received
- Must report to the DCC within 5 calendar days of becoming aware of the UP

Tasks

- Unanticipated problems are to be reported within 5 calendar days to the ACRC Clinical Center. To report, key the Unanticipated Problem (UP) form at www.cctirals.org/alaacrc; include as much information as possible. Key within 5 calendar days even if some data is missing.
- Contact the DCC if UP is not acknowledged within 3 business days of submission
- Submit new information and/or follow-up information by editing the form, including resolution of event.

Forms (abbreviation)

- Unanticipated Problem Report (UP)

6.5. Protocol deviations: definition and reporting

Purpose

- To report an occurrence of a protocol deviation

Definition

- Protocol deviations include minor or administrative departures from the protocol procedures approved by the IRB that are not serious are reported on the Protocol Deviation (PD) form.
 - Example: Spirometry test not performed according to protocol
 - Out of window visits do not need to be reported on PD form to the DCC (DCC will determine out of window visit status from data keyed into the data system)
- Protocol deviations that are serious (i.e., involve increased risk) are reported as unanticipated problems in an expedited manner. Protocol deviations should be reported on the UP form, if they meet the following three criteria:
 - The protocol deviation increases the chance of risk for the participant
 - The protocol deviation is unexpected
 - The protocol deviation is related to the research

When

- As needed, whenever a protocol deviation is first reported or discovered or whenever follow-up information is received
- Must report to the DCC within 10 calendar days of becoming aware of the PD

Tasks

- Protocol deviations are to be reported within 10 calendar days to the ACRC Clinical Center. To report, key the Protocol Deviation (PD) form at www.clinicaltrials.org/alaacrc; include as much information is possible. Key within 10 calendar days even if some data is missing
- Submit new information and/or follow-up information by editing the form

Forms (abbreviation)

- Protocol Deviation (PD)

7. Data collection and forms completion

7.1. List of forms, questionnaires, logs

Forms/Log name	Abbreviation	Data entered
Forms		
Baseline Asthma and Medical History	BA	✓
Biospecimen Collection	BC	✓
Clinic Visit	CV	✓
Drug Dispensing	DA	✓
Drug Return/Capsule Count	DR	✓
Early Study Exit	EE	✓
Eligibility	EL	✓
Instructions for TRIM Diary Cards	IDC	No
Instructions for Measuring Peak Flow	IPF	No
Instructions for Methacholine Challenge Test	IMC	No
Methacholine Challenge Testing	MC	✓
Missed Data	MD	✓
Participant Information	PI	No
Physical Exam	PE	✓
Protocol Deviation Form	PD	✓
Physical Measurements	PM	✓
Pulmonary Function	PF	✓
Screening	SC	✓
Serious Adverse Event Report	SR	✓
Study Evaluation	EV	✓
TRIM Diary Card	DC	✓
Treatment Termination	TT	✓
Unanticipated Problem	UP	✓
Unmasking	UM	✓
Questionnaires		
Asthma Control Test (ACT)	TA	✓
Asthma Symptom Utility Index (ASUI)	AS	✓
Gastrointestinal Symptom Rating Scale (GSRS)	GS	✓
Marks Asthma Quality of Life Questionnaire (MAQL)	MQ	✓
Patient Health Questionnaire (PHQ-9/GAD-7)	HQ	✓
Quality of Life by RAND Health (SF-36V1)	SF	✓
Suicide Screening Worksheet (SSW)	SSW	✓

Logs/Administrative Forms		
ACRC General Supply Order Form	GO	No
Asthma and Allergy Medications Log	AA	✓
Medications Log (non-asthma/non-allergy)	CM	✓
Participant Screening Log	PS	✓
TRIM Supply Order Form	IO	No
Clinical Center Certification		
ACRC Personnel Assurance Statement	PA	No
TRIM Clinical Center Certification	CC	No
Personnel Certification	CE	No
TRIM Methacholine Challenge Test Assurance Statement	MA	No
TRIM Satellite Center Certification	CT	No
TRIM Spirometry Test Assurance Statement	SA	No
TRIM Signature and Delegation of Duties	SD	No

7.2. ID codes

Codes

- Reference #
- Participant ID
- Alpha ID code
- Visit
- Personnel Identification Number (PIN)
- Clinical Center ID

Reference

- A unique identification code assigned by the data system after the second keying of a form is completed
- Recorded on form (upper-right hand corner of first page) by data entry personnel after form is entered into database

Participant ID

- 5-digit center specific alphanumeric code taken sequentially from the sheet of Clinic Labels
- Distributed to the ACRC Clinical Center by the Data Coordinating Center (see example in Section 7.2.1)
- Unique # assigned to each potential participant who starts the Screening Visit (V1)
- All participant forms will be identified by that #

Alpha ID code

- 5-character code, unique for every participant enrolled at a site
- Assigned by coordinator at participant registration
- Site to determine an assignment scheme
 - i.e., can use a 5-letter word
- It is strongly suggested that the unique participant ID and participant's name **NOT** be included in this code

Visit

- May be pre-printed on the form or label by the DCC or hand recorded
- Screening visit (first clinic visit) = V1; Follow-up visit = V2
- N = not associated with a study visit; e.g., Serious Adverse Event Report

Personal Identification Number (PIN)

- Unique 3-digit alpha-numeric identification code for each clinic staff member completing data forms; First letter is the site letter
- Staff members must be "registered" by being entered in the online directory (by Lead Coordinator) for a PIN to be generated
- Assignment of PIN automatically generates temporary passcode, "changeme"
- Lead Coordinator can reset passcode to "changeme", if passcode is forgotten

Clinical Center ID

- 2-4 letter code identifying primary ACRC Clinical Center site
- All satellites should use code of primary site

Table 3: Clinical Center ID and Designated Participant ID Letter

Clinic ID	Name of Clinical Center	Center Director	Designated letter for participant IDs
DUKE	Duke University Medical Center	Loretta Que, MD	B
IC	Northwestern	Ravi Kalhan, MD	D
NJC	National Jewish Health	Barry Make, MD	L
NNEC	Northern New England Consortium	Charles Irvin, PhD	M
UAZ	University of Arizona	Lynn Gerald, PhD	V

7.2.1. Example of a clinic label sheet

Clinics will receive a sheet of participant ID labels at the start of the trial. A participant's ID will start with "T" (for TRIM), followed by your assigned clinic letter and 3 numbers starting at 100 and continuing sequentially.

To assign a participant ID, attach the next sequential label to item #2 on the participant's Screening form (SC).

TRIM Clinic Label Sheet (example)

TZ100	TZ101	TZ102
TZ103	TZ104	TZ105
TZ106	TZ107	TZ108
TZ109	TZ110	TZ111
TZ112	TZ113	TZ114
TZ115	TZ116	TZ117
TZ118	TZ119	TZ120
TZ121	TZ122	TZ123

7.3. Completing forms

General guidelines

- Use dark blue or black ink
- Written responses should be legible to other people
- Limit use of abbreviations
- All completed forms should be reviewed by clinic coordinator to ensure that
 - All items are answered
 - Written responses are legible
 - Data are consistent
- Never change the wording of questions, decimal places, or the unit for a response that is pre-coded or printed on a form
- A response space should have only one letter or digit per space
- Numeric responses are to be right justified with all spaces completed. Use lead zeros as necessary. Example: 0 0 3 2
- Alpha or alphanumeric responses are to be left justified. If blank spaces remain, leave them blank. Example: P 1 2 _; D C C
- Data on forms should always match database

Error correction

- Do not obliterate erroneous responses
- Never use correction fluid or tape or erase a response
- Draw a single line through incorrect response and indicate correct response clearly, above or next to the erroneous response; the erroneous response should be readable
- Use a different color ink; e.g., green or red, to make edits
- Staff member making changes to a form should initial and date each change in the margin and provide a brief explanation for the change; e.g., “error”, “participant changed mind”
- Be sure that the database is updated with the revised information

Rounding rules

- Responses should have only one letter or digit per space
- The number of spaces or location of a decimal point on a form should not be added or changed. If you think there is an error in the format of a response field, e.g., not enough spaces to the left of decimal point, please alert the DCC as soon as possible.
- If a response has a greater number of digits to the right of a decimal point than spaces allow, the response should be rounded as follows:
 - If the first digit following the last data space is less than 5, round down; e.g., if the form has spaces for a 2 digit response with one decimal between the digits (_ . _), then 4.71 would be rounded to 4.7 and 4.14 would be rounded to 4.1
 - If the first digit following the last data space is 5 or more, then round up; e.g., if the response field is for 2 digits with a decimal between the digits (_ . _), then 4.78 and 4.75 would be rounded to 4.8 and 4.15 would be rounded to 4.2

- More examples:
 - For a response field of three digits (__ __ __), 79.485 would be recorded as 079 and 79.584 would be recorded as 080
 - For a response field of (__ . __ __), 4.2745 would be recorded as 4.27 and 4.2754 would be recorded as 4.28
- **Note: Do not round responses unless the number of digits in a response field requires it. Otherwise, record data as collected.**

If there are more whole integer digits than the response field allows, contact the Data Coordinating Center.

7.4. Distributed data entry

7.4.1. Logs/Administrative forms

Purpose

Provide records of the dispensation of drug, medications taken by the participant, participants screened for the trial, transmission of specimens, and supplies ordered.

Tasks/Timeframe

- **ACRC General Supply Order Form (GO)** is used to order general ACRC supplies
- **Asthma and Allergy Medications Log (AA)** is used to record all asthma and allergy medications used by the participant during TRIM
- **Medications Log (non-asthma/non-allergy) (CM)** is used to record all non-asthma/non-allergy medications used by the participant during TRIM.
- **Participant Screening Log (PS)** maintained during the entire trial to record all participants screened for the study; all reasons for screen failures to be recorded
- **TRIM Supply Order Form (IO)** is used to order supplies specific to the TRIM trial

7.4.2. Certification forms and consent

Purpose

- To assure that all necessary facilities, equipment, personnel, and approvals are in place before TRIM is open to participants

Tasks

- **TRIM Clinical Center Certification (CC)** is to be completed by the Lead ACRC Coordinator and signed by the Center Director after all arrangements for the conduct of TRIM are in place before site.
- **TRIM Spirometry Test Assurance Statement (SA)** is to be signed by Center Director as assurance that spirometry testing is being conducted per TRIM protocol. Signed statement sent to DCC and a copy is kept by clinic.
- **TRIM Methacholine Challenge Test Assurance Statement (MA)** is to be signed by the Principal Investigator as assurance that methacholine challenge testing is being conducted per TRIM protocol at all ALA-ACRC TRIM clinical centers. The original should be sent to the DCC and a copy should be kept by clinic.
- **TRIM Satellite Center Certification (CT)** is to be signed by satellite Co-PI and Lead Coordinator as assurance that required personnel are trained and ready at satellite. Signed statement sent to DCC via ACRC Clinical Center and a copy is kept by satellite.
- **Personnel Certification form (CE)** is to request certification for one or more TRIM functions. It is to be filled out by any staff member that will perform TRIM functions.
- **TRIM Signature and Delegation of Authority (SD) log** is to be filled for each person working on TRIM, and is to be signed off by the Site PI/Center Director. The log is to be updated throughout the trial.
- **ACRC Personnel Assurance Statement (ACRC form PA)** is to be completed by all personnel involved with ACRC studies. The ACRC PA form need only be completed once to cover all ACRC studies. Should be completed before individual is entered in the ACRC Directory.

Consents

- **Research Subject Information and Consent Form** is read and signed by the participant. Co-signed by person obtaining consent and PI (if someone different than person obtaining consent).

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7.5. Distributed data entry

Online data system background

- Distributed data entry for the ALA-ACRC TRIM trial will be conducted via the internet
- Data will be double entered to ensure accuracy
- Error and consistency checks will be built-in to the data entry application
- The data entry application and clinical data will be secured with passwords and user names stored in the TRIM database
- Data will be stored in redundant databases residing on a web server in a password-protected area.
- Data will be archived daily to a computer at the DCC
- The DCC will conduct audits of ACRC Clinical Center data during the course of the trial

Purpose

- To collect all trial data
- To track participant activity
- To monitor ACRC Clinical Center performance

Tasks/Timeframe

- ACRC Clinical Center staff will log into the data entry system on the TRIM web site at <http://www.jhcct.org/Secure/TRIM/TRIMHome.asp>
- ACRC Clinical Center staff will be assigned an ACRC Personal Identification Number (PIN) and password that will be required for data entry and will limit access to only their clinic's data
- Once logged into the data entry section, users will be able to:
 - Register a new participant
 - Enter/edit data for an existing participant
 - View reports for their clinic
- Participants must be registered before any forms can be entered for that participant; registration consists of creating a record for a new patient including his/her TRIM ID and name code
- Forms should be keyed within 10 working days of collection unless otherwise indicated
- While keying these forms, ACRC Clinical Center staff will be prompted regarding **errors** (which must be corrected) and **warnings** (which should be checked, but may not require correction)
- Data should be edited as necessary for form corrections or edit requests from the DCC
- Forms should be retained by clinics in an accessible location
- ACRC Clinical Center staff should check the reports for their clinic at least twice per week. These pages will include real-time recruitment reports, forms status, and other information
- A Data System Manual is posted on the TRIM website for ease of access
 - If there is a problem with data entering information, then complete a Data Feedback form (available in the data system)

8. Communication prototypes

Purpose

- To communicate with participant and participant's primary care provider regarding participation in TRIM

When

- Appropriate letter(s) to be sent when participant randomized into trial and when participation in trial ends

Supplies

- Prototype communications are included. The letters you will use are to have your institution's requisite approvals.

8.1. Physician communication introduction letter

Dear Dr(s). _____:

Your patient, _____, was recently enrolled in the clinical trial, Trial of Roflumilast in Asthma Management (TRIM). This study is a randomized, double-masked, placebo-controlled study designed to determine the effectiveness and tolerability of roflumilast in treatment of poorly controlled asthma in obese participants. If successful, roflumilast would represent a new treatment for obese patients with asthma, a patient population known to be resistant to current therapies. Eligible participants are those with a physician diagnosis of asthma on regular controller therapy for at least 3 months; a past, or current, positive methacholine challenge test; 18 years or older; a BMI > 30 kg/m²; and poorly controlled asthma defined by, Asthma Control Test Score < 20, or use of rescue inhaler, on an average of > 2 uses/week for preceding month, or nocturnal asthma awakening, on an average of 1 or more times / week in preceding month, or ED/hospital visit or prednisone course for asthma in past six months.

Your patient was randomly assigned to receive either roflumilast or placebo. Your patient has started on one tablet every other day (roflumilast 500 µg or placebo). If your patient tolerates the dose, he/she will be instructed to take one tablet every day (500 µg of roflumilast or placebo) over the course of the study. If your patient cannot tolerate this dose, we will ask them to continue in the study taking one tablet every other day. The trial will collect information including demographics, medical history, lung function, and questionnaires. Your patient will be followed for approximately 24 weeks.

Your patient should continue to use you as their primary care physician.

The dose of roflumilast used in this study is well tolerated, with the most likely side effects consisting of diarrhea, nausea, insomnia, headache, dizziness. There have been some reports of patients experiencing psychiatric adverse events such as anxiety, depression, insomnia, and suicide.

At the end of the study, your patient will learn which study treatment he/she received, and will be given a copy of the pulmonary function test results from the final visit. Your patient will be told that he/she may contact our clinic for emergencies, if necessary, during the interim period. Please feel free to contact our clinic (xxx-xxx-xxxx) or me personally if you have any questions.

Sincerely,

Principal Investigator
Institution Name

8.2. Participant release to share results letter

Prototype: Participant release to send spirometry results to primary care providers

CONSENT TO RELEASE RESEARCH SUBJECT BREATHING TEST FORM

Title: Trial of Roflumilast in Asthma Management

Protocol No.: IRB Name Protocol # XXXXX

Funding Source: The National Heart, Lung, and Blood Institute (NHLBI) and the American Lung Association (ALA)

Investigator: <<Site Investigator>>

Site(s): <<Site name>>
<<Site address>>
<<Site city, state, zip>>

**STUDY-RELATED
PHONE NUMBER(S):** Research study questions
<<Site Investigator>>
<<Investigator Phone>>

Research-related injury
<<Site Investigator>>
<<Investigator Phone>>
<<Investigator Phone, 24 hours>>

SUBINVESTIGATOR(S) : <<Site Investigator>>

Permission to Notify Physician(s):

I give permission for study personnel to fax/send my breathing test results to my primary care physician.

Printed Name of Subject

Signature of Subject

Date

CLINIC SIGNATURE(S)

Signature of Person Conducting Informed Consent
Discussion

Date

Signature of Investigator (if different from above)

Date

8.3. Physician exit letter (for use after participant has been randomized)

Dear Dr(s). _____:

Your patient, _____, recently completed participation in the clinical trial, Trial of Roflumilast in Asthma Management (TRIM). This study is a randomized, double-masked, placebo-controlled study designed to determine the effectiveness and tolerability of roflumilast in treatment of poorly controlled asthma in obese participants. If successful, roflumilast would represent a new treatment for obese patients with asthma, a patient population known to be resistant to current therapies. Eligible participants are those with a physician diagnosis of asthma on regular controller therapy for at least 3 months; a past, or current, positive methacholine challenge test; 18 years or older; a BMI > 30 kg/m²; and poorly controlled asthma defined by, Asthma Control Test Score < 20, or use of rescue inhaler, on an average of > 2 uses/week for preceding month, or nocturnal asthma awakening, on an average of 1 or more times / week in preceding month, or ED/hospital visit or prednisone course for asthma in past six months.

Your patient has now completed all study visits and has received an envelope indicating the assigned study treatment and the results from his/her last pulmonary function test. We have counseled your patient to show you the treatment assignment and the results of his/her final spirometry tests.

We hope participation in this clinical trial was beneficial to your patient. Please contact our clinic (xxx-xxx-xxxx) or me personally, with any questions.

Sincerely,

Principal Investigator

Institution Name

8.4. Participant exit letter

Dear _____,

Thank you for participating in the clinical trial, Trial of Roflumilast in Asthma Management (TRIM). This study is trying to determine the effectiveness and tolerability of roflumilast in treatment of poorly controlled asthma in obese participants.

The treatment group you were assigned to is in the enclosed, sealed envelope. We have also provided the results of your final pulmonary function test (breathing test). We recommend that you show your primary care provider the results of your final pulmonary function test.

There are other participants in the study, enrolled after you, who are still being treated and followed. It is important that you do not inform me, the other study personnel, or other study participants what treatment you were assigned because the study is still collecting information on these people. We make it a point not to know what treatment participants are assigned during the study so that knowledge of the treatment assignment does not influence the data we are collecting.

Again, thank you for your participation in TRIM.

Sincerely,

Principal Investigator
Institution Name

Enclosures:
Treatment assignment envelope
Results of final pulmonary function tests

9. Quality assurance

ACRC clinical center responsibilities

- A clinical center is comprised of one main ACRC Clinical Center which may have additional satellite clinics associated with it
- The ACRC Clinical Center staff must include a Principal Investigator, Study Physician, Lead Coordinator, Data System Operator, and Spirometry Tester. Staff may carry out the duties for more than one role, but additional staff members are recommended.
- The main ACRC Clinical Center is responsible for distributing supplies to satellites
- The Lead Coordinator (main ACRC Clinical Center) is responsible for
 - Upkeep of the ALA-ACRC web-based directory for the main ACRC Clinical Center and all satellites
 - Changes to the ALA-ACRC web-based directory can be made by the Lead Coordinator only
 - Distribution of correspondence (e.g., PPMs, DSMB memos) and study materials to all other staff members at the main ACRC Clinical Center and satellite clinic(s) as appropriate
- The Principal Investigator is responsible for the distribution of correspondence and study materials to other study investigators at the main ACRC Clinical Center and satellite clinic(s) as appropriate

Satellite clinics

- Satellite clinics are an adjunct to their main ACRC Clinical Center (see end of Section 7.2 for list of main ACRC Clinical Centers and respective ID codes)
- Each satellite clinic is to have a coordinator who is responsible to the Lead Coordinator at the main ACRC Clinical Center
- Other study personnel (e.g., Data System Operator) are highly recommended but optional and at the discretion of the satellite clinic and main ACRC Clinical Center
- Forms for study visits conducted at a satellite clinic are to be completed and maintained at the satellite
- All study procedures performed by the satellite clinic must conform to the TRIM protocol and Manual of Operations (MOP)

9.1. Data audits and data quality queries

On-going data audits

- Periodically during and after the clinical phase of the trial, the DCC will audit clinic data
 - DCC will send an email to a clinic requesting copies of forms for particular participant(s)
 - Within 2 weeks the clinics should send copies of the requested forms via email or FedEx (FedEx account number to be distributed to clinics)
 - The DCC will review the data on the paper form and compare it to entries in the data system

Data Quality Queries (DQQs)

- The DCC will generate a Data Quality Query (DQQ) for any discrepancy found during an audit. A separate DQQ is created for each discrepancy found in a form
- All DQQs will be posted on the DQQ Management System. To get to the DQQ page go to the TRIM website, <http://www.jhcct.org/Secure/TRIM/TRIMHome.asp> and follow the link to the Data System page
- Clinics will receive a pop-up message alerting them that new DQQs are posted
- Clinics should respond to the posted DQQs
 - After reviewing the DQQs, investigate the problem (usually by inspecting the source document) and make any necessary changes to the data system, the paper form, or both
- Changes to the paper form must be made according to the error correction procedures outlined in Section 7.3.
- Changes in the data system
 - After necessary changes to paper forms have been made, go to the DQQ page, click on “View/Edit DQQ,” choose one of the available options to indicate how the DQQ has been resolved (i.e., data system edited, data form altered, etc.) and click “Submit” button. The DQQ will be removed from the clinic’s DQQ list
 - Contact the DCC at JHSPH.ala-acrc@jhu.edu with questions concerning the proper resolution of a DQQ
- Many coordinators find it easiest to go to the DQQ page, print out their list of pending DQQs, investigate and resolve each one, and mark on the paper list how each DQQ has been resolved. Then they go back to the DQQ system and mark each as resolved by choosing and submitting the appropriate response.

10. References

10.1. Frequently used acronyms

ACRC	Airways Clinic Research Center
AE	Adverse event
ALA	American Lung Association
BD	Bronchodilator
COCO	Chronic Refractory Cough Cohort Study
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed tomography scan
CD	Cough Diary
DCC	Data Coordinating Center
DQQ	Data Quality Queries
DSMB	Data and Safety Monitoring Board
DSO	Data System Operator
EC	Executive Committee
FAQ	Frequently Asked Questions
FEV₁	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GEN	General Knowledge Assessment, study specific
GERD	Gastroesophageal Reflux Disease
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
MOP	Manual of Procedures
NHLBI	National Heart, Lung, and Blood Institute
NSR	Non-significant risk
PFT	Pulmonary function test
PI	Principal Investigator
PIN	Personal identification number
PPM	Policy and Procedure Memoranda
QOL	Quality of Life
SAE	Serious adverse event
SC	Steering Committee
SOV	Schedule of visits
TRIM	Trial of Roflumilast in Asthma Management
UP	Unanticipated Problem
VAS	Visual analog scale

11. Appendix

A. List of acceptable asthma controller therapy drugs

Drug Class	Brand name	Generic Name
Anti-IgE injections	Xolair	Omalizumab
Anti-IL5	Nucala	mepolizumab
	Cinqair	reslizumab
	Fasenra	Benralizumab
Inhaled anticholinergic bronchodilators	Atrovent	Ipratropium bromide
	Spiriva Respimat	Tiotropium bromide
	Spiriva Handihaler	Tiotropium bromide
Inhaled combination corticosteroid plus long-acting beta-agonist	Advair	Fluticasone/Salmeterol
	Dulera	Mometasone/Formoterol
	Symbicort	Budesonide/Formoterol
	Breo-Ellipta	Fluticasone furoate and vilanterol
Inhaled corticosteroids	Aerospan	Flunisolide
	Alvesco	Ciclesonide
	Asmanex	mometasone
	Flovent	Fluticasone
	Pulmicort	Budesonide
	Qvar	Beclomethasone
Combination short acting beta agonist and anticholinergic	Arnuity Ellipta	Fluticasone/furoate
	Duoneb	Albuterol/Ipratropium combination
	Combivent Respimat	Albuterol/Ipratropium combination
Inhaled long-acting beta-agonist bronchodilators	Brovana	Arformoterol
	Foradil	Formoterol
	Perforomist	Formoterol
	Arcapta neohaler	Indacaterol
	Striverdi Respimat	Olodaterol
	Serevent	Salmeterol
Inhaled short-acting bronchodilators	ProAir	Albuterol
	Proventil	Albuterol
	Ventolin	Albuterol
	Xopenex	Levalbuterol
Oral Anti - Leukotrienes	Accolate	Zafirlukast
	Singulair	Montelukast
	Zyflo	Zileuton
Oral corticosteroids	Cortan	Prednisone
	Decadron	Dexamethasone
	Delta-Cortef	Prednisolone
	Deltasone	Prednisone
	Dexone	Dexamethasone

	Dexpak	Dexamethasone
	Medrol	Methylprednisolone
	OraPred	Prednisolone
	Orasone	Prednisone
	Pepiapred	Prednisolone
	Predniscen-M	Prednisone
	Prelone pills or liquids	Prednisolone
	Solurex	Dexamethasone
	Steraped	Prednisone

B. Instructions for TRIM Diary Cards



TRIM

Instructions for TRIM Diary Cards

Morning

Fill out the following information:

1. Date

- Record the date. Be sure to start recording your information under the correct date and day column and continue from that point. Dates can be printed out for you at the clinic.

2. Morning peak flow

- Do 3 peak flows (standing) before taking any asthma medications. Perform according to the instructions provided to you.
- Enter the highest of the 3 peak flow measurements.

3. Awakened by asthma last night

- Check (✓) if you were awakened by asthma last night, otherwise leave blank
- Consider last night to be the time you went to bed until you got up the next morning.
- If you were awakened last night due to reasons other than asthma, leave blank.

	Mon	Tue	Wed	Thur	Fri	Sat	Sun
1. Date (month/day):	__-__	__-__	__-__	__-__	__-__	__-__	__-__
2. Morning peak flow (highest of 3, before bronchodilator):							
For item 3 check (✓) if occurred							
3. Awakened by asthma last night:	()	()	()	()	()	()	()

Evening

Fill out the following information considering events that occurred throughout the entire day:

4. Drug use for quick relief of asthma symptoms

- Do record any use of rescue medication or inhalers for relief of asthma symptoms since last evening (e.g., Ventolin, albuterol)
- Do NOT enter use of rescue medication when taken to prevent symptoms, for example, before exercise.

4a. # puffs per day by metered dose inhaler

- Enter the total number of inhaler puffs for relief of asthma symptoms during the indicated day.
- Enter "0" if no rescue medication was used.
- Example: if you used your inhaler twice in one day, and took two puffs each time, you should record 4 puffs for that day

4b. # uses per day by nebulizer

- Enter the number of nebulizer uses for relief of asthma during the indicated day.
- Enter "0" if no rescue medication was used.

	Mon	Tue	Wed	Thur	Fri	Sat	Sun
4. Drug use for quick relief of asthma symptoms (do not count uses to prevent symptoms, for example before exercise; if none record as "0")							
a. # puffs per day by metered dose inhaler:							
b. # uses per day by nebulizer:							

5. **Used oral or IV prednisone/steroids for asthma**
 - Check (✓) if you took oral or IV steroids for asthma symptoms (eg, prednisone, prednisolone), otherwise leave blank
6. **Used inhaled corticosteroid (e.g. daily controller meds, albuterol, advair)**
 - Check (✓) if you took inhaled corticosteroids for asthma symptoms (e.g., before exercise) otherwise leave blank
7. **New or increased dose of asthma medicine**
 - Check (✓) if you started using a new asthma medication or started an increased dose of an asthma medication you were currently using, otherwise leave blank.
 - Do NOT include:
 - rescue medications (already listed in item 4a and 4b)
 - oral or IV prednisone/steroids for asthma (already listed in item 5)
8. **Urgent unscheduled healthcare contact for asthma**
 - Check (✓) if you went to a hospital, emergency room, a clinic or a doctor's office because of asthma symptoms, otherwise leave blank.
 - Do NOT include routine medical visits (e.g. physical exam, regularly scheduled followup appointment).

For items 5 - 8 check (✓) if occurred today	
EVENING	5. Used oral or IV prednisone/steroids for asthma: () () () () () () ()
	6. Used inhaled corticosteroid (e.g. daily controller meds, albuterol, advair): () () () () () () ()
	7. New or increased dose of asthma medicine other than drugs listed in 4a, 4b, 5, or 6: () () () () () () ()
	8. Urgent unscheduled healthcare contact for asthma (ED/hospital/clinic or doctor visit): () () () () () () ()

9. **Asthma score**
NOTE: An asthma episode is a single period with one or more asthma symptoms, such as wheezing, coughing, chest tightness, or shortness of breath.
 - Enter the code that best describes your asthma for the indicated day (# of episodes and severity of them)
Examples:
-Awakened from sleep because of asthma symptoms that lasted less than 2 hours = 2
-An episode lasting more than 3 hours = 3

EVENING	
	9. Asthma score: 0 – No asthma episodes 1 – 1-3 asthma episodes, each lasting 2 hours or less -- all mild 2 – 4 or more mild asthma episodes, or 1 or more asthma episodes that interfered with activity, play, school, or sleep for less than 2 hours 3 – 1 or more asthma episodes which last longer than 2 hours, or result in shortening normal activity, seeing a doctor, or going to a hospital

Instructions to return diary cards

Bring all completed diary cards to the next clinic visit. Questions? Call _____

C. Instructions for Measuring Peak Flow



TRIM

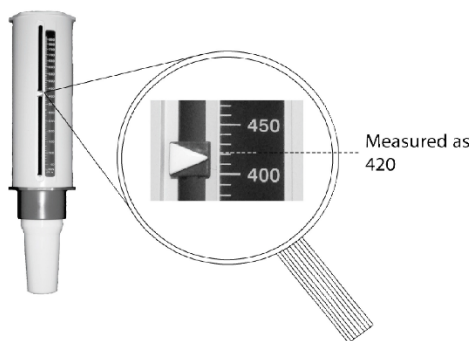
Instructions for Measuring Peak Flow

When:

- You should measure your peak flow each morning.
- You should also measure your peak flow anytime you are having asthma symptoms. If you have asthma symptoms and your peak flow is decreased, you should follow the instructions on your Asthma Action Plan Card.
- The measurement should be taken before you take any asthma medications. If you took asthma medications during the day or night, try to measure your peak flow at least 6 hours after you took that medication and before you take any medication in the morning.

Instructions for Measuring Peak Flow

1. Stand up and relax. You should always measure your peak flow in the same position.
2. Set the pointer to the end of the scale near the mouthpiece. Be sure your fingers do not obstruct the slot in which the pointer slides or the end where the air comes out.
3. Hold the meter lightly so that you do not obstruct the slot in which the pointer slides. Be sure to point the meter straight out, parallel to the ground.
4. Take as deep a breath as possible then place the peak flow mouthpiece in your mouth making sure to form a tight seal with your lips.
5. Blow into the peak flow meter as quickly and as hard as you can. The correct method is a quick, hard blow, rather than a long slow exhalation. Peak flow measurements vary a lot depending on how much effort you put into it. This means that you must always try to blow as hard as you can to have good, consistent results.
6. The pointer will slide up the slot and stop at a number corresponding to your Peak Expiratory Flow (PEF) for that test. Make a note of the reading.
7. Return the pointer to the mouthpiece end of the scale and repeat steps listed above 2 more times to obtain 3 readings. Record the highest of the 3 readings on the diary card. You may rest between trials if you wish.



Make a note of the reading that corresponds to your Peak Expiratory Flow (PEF)



Hold the peak flow meter straight out, parallel to the ground

AMERICAN LUNG ASSOCIATION Airways Clinical Research Centers (ALA-ACRC)
Trial of Roflumilast in Asthma Management (TRIM)

TRIM

You are scheduled for a Methacholine Challenge Test on:

Location: _____

Telephone #: _____ - _____ - _____

1. Do not smoke 1 hour before testing.
2. Do not drink alcohol 4 hours before testing.
3. Do not take medications that affect lung function, see list and record below.

You may use your rescue medication because of asthma symptoms, if needed. Please call to let the clinic know what you took before coming in for your visit. Your appointment may need to be rescheduled.

- **Short-acting bronchodilator for at least 6 hours** before your test
 - Examples: albuterol, Ventolin, Proair, Proventil, Xopenex, isoproterenol, metaproterenol

Your medication: _____

- **Medium-acting bronchodilator for at least 12 hours** before your test
 - Examples: ipratropium, Atrovent, Apovent, Ipraxa, Rinatec

Your medication: _____

- **Oral theophylline for at least 12-24 hours (0.5-1 days) before your test**
 - Examples: Theo-Dur, Theo-24, Elixophylline, Theochron, Uniphyll

Your medication:

- **Long-acting bronchodilator** for at least **36 hours (1.5 days)** before your test
 - Examples: Salmeterol, Formoterol, Advair, Serevent, Symbicort, Dulera

Your medication: _____

- **Ultra-long-acting bronchodilator for at least 48 hours (2 days) before your test**
 - Examples: indacaterol, Arcapta Neohaler, vilanterol, olodaterol, Striverdi Respimat

Your medication: _____

- **Long-acting anti-muscarinic agents for at least 7 days (1 week) before your test**
 - Examples: tiotropium, Breo Ellipta, Spiriva, aclidinium

Your medication:

E. Drug information sheet template

Information Sheet about Study Drugs

What drugs are being studied?

You have been randomized (assigned by chance) to receive one of the following:

- Roflumilast OR
- Placebo, a placebo is an inert substance with no known biological activity, like a sugar pill

What is roflumilast?

Roflumilast is a prescription medication used in adults with chronic obstructive pulmonary disease (COPD), it reduces inflammation in the lungs.

Roflumilast also has metabolic effects that may be helpful for patients with asthma who are overweight. It can induce weight loss, which may also lead to improved asthma control.

How do you take your study drug?

You will start by taking one tablet every other day. After the first two weeks, if you tolerate 1 tablet every other day, you will start taking one tablet every day. Take the medication exactly as the study physician tells you. It can be taken with or without food.

When to take study drug	Number of tablets	Dose
First 2 weeks	1	500 mcg, every other day
Week 3 to the end of the study	1	500 mcg, every day

How do I store the study drug?

Store the study drug at room temperature (68° to 77°F) away from moisture.

What are the side effects of roflumilast?

The most common side effects are diarrhea, weight loss, nausea, headache, back pain, flu like symptoms, problems sleeping (insomnia), dizziness, and decreased appetite. Roflumilast has been associated with psychiatric side effects such as insomnia, anxiety, depression, and thinking about suicide. Be sure to tell the study physician if you experience any of the side effects listed above.

What if I miss a dose?

If you miss a dose, take the missed dose as soon as you remember. Skip the missed dose if it is almost time for your next scheduled dose. Do not take extra medicine to make up the missed dose and never take more than 1 tablet in a 24 hour period.

How does the study drug interact with other drugs?

Roflumilast may affect the way other medicine work, and other medicines may affect how roflumilast works. Because you do not know whether you are taking roflumilast or placebo, do not take any new prescriptions, over-the-counter medications, herbal medicines, or nutritional supplements without telling the study physician. Also, tell your primary doctor that you are taking this study drug.

What do I do with unused study drug?

Please bring all study drug bottles and any unused drug with you each time you have a study visit. If you forget, return the bottle at the following visit. Do not mix tablets from different bottles.

Where can I get more information?

Study physician contact information to be inserted here

F. Fasting blood sugar sample letter

Insert letterhead/Institution logo here

"Patient's name"

"Patient's address"

"Patient's address line 2"

3 January 2020

Dear *"Patient's name"*,

Thank you for participating in our Trial of Roflumilast in Asthma Management (TRIM) pilot study. This letter is to inform you of the results of your fasting blood glucose test done on *"WEEK DAY, MONTH DAY, YEAR"*.

"Value" mg/dl

Less than 100 mg/dl is normal: you do not need to do anything. If your level is 100-126, we recommend you follow-up with your primary care provider within the next 3 months to discuss, as this is just above the upper limit of normal.

If you consented to incidental findings from your participation in this study to be reported to your primary care physician, they will be notified of these results as well. If you have any additional questions or concerns, please feel free to contact your primary care physician or *"Study Physician"* at *"XXX-XXX-XXXX."*

Sincerely,

"Study Physician's signature"

Study Physician

Title

Address

Phone number

Email

G. Unmasking letter

Dear TRIM study participant,

Thank you for your participation in the Trial of Roflumilast in Asthma Management study (TRIM). You have now completed all study visits for the trial and we appreciate the time and effort you took to help us investigate how effectively roflumilast might work for people with poorly controlled asthma and an increased BMI. Because you have completed the study, we are now able to inform you of the treatment you received during the trial, either roflumilast or placebo (“sugar pill”).

Your treatment assignment is located in the envelope the study team member will give to you. **Please do not open the envelope until after you have left your final visit.**

We encourage you to show this letter to your primary care physician to discuss how this may impact your future care. However, we ask that you do not share or discuss which treatment you received with any of the TRIM study team members or other TRIM study participants you may know. We do not want the study staff or volunteers still participating in the study to know what treatment you received.

Again, we sincerely thank you for your participation in the TRIM study and we are very grateful for your time.

Sincerely,

TRIM study team

H. Recruitment scripts

Example script for approaching potential participants with elevated BMI.

“I’m reaching out because you have asthma and you might be a good candidate for one of our research studies. We recognize that people with poorly controlled asthma also may have trouble managing their body weight. Are you interested in hearing more about what the study entails.”

And/or

“We are contacting you about a study we are doing to try to understand why some people have severe, difficult to control asthma. It’s recently been discovered that people with asthma have an increased risk of gaining weight, and then gaining weight makes their asthma difficult to control, which can lead to a vicious cycle of weight gain and more asthma symptoms. This can be a really difficult problem to deal with, and so the ALA ACRC is working to find new treatments that might be more effective particularly in people who have a BMI of 30 or more, which is actually the majority of people with severe asthma. Are you interested in hearing more about what the study entails.”

I. TRIM schedule of visits

TRIM Schedule of Visits

Thank you for joining TRIM! This sheet tells you the date and time of each visit and what will happen at each visit. Remember, if you are having asthma symptoms, you should use your rescue inhaler as instructed in your Asthma Action Plan Card.

Carry with you at all times	Bring to each clinic visit	Diary Cards
- Asthma Action Plan Card - Rescue medications	- Study drug - Peak flow meter - Completed diary cards	Fill out each morning and evening

Visit 1

Date/time: _____

- Informed consent
- Instructions in study procedures
- Medical history
- Physical exam (*if necessary*)
- Pregnancy test (*if applicable*)
- Questionnaires
- Breathing tests
- Physical measurements
- Action Asthma Plan Card/Peak flow meter

Visit 2

Date/time: _____

- Bring diary cards and peak flow meter
- Pregnancy test (*if applicable*)
- Blood draw
- Health history
- Questionnaires
- Breathing tests
- Physical measurements
- Distribution of study drug

Visit 3

Date/time: _____

- Bring diary cards, peak flow meter, and study drug
- Pregnancy test (*if applicable*)
- Health history
- Questionnaires
- Breathing tests
- Physical measurements

Visit 4

Date/time: _____

- Bring diary cards, peak flow meter, and study drug
- Pregnancy test (*if applicable*)
- Health history
- Questionnaires
- Breathing tests
- Physical measurements
- Distribution of study drug

Visit 5

Date/time: _____

- Bring diary cards, peak flow meter, and study drug
- Pregnancy test (*if applicable*)
- Health history
- Questionnaires
- Breathing tests
- Physical measurements
- Distribution of study drug

Visit 6

Date/time: _____

- Bring diary cards, peak flow meter, and study drug
- Pregnancy test (*if applicable*)
- Health history
- Questionnaires
- Breathing tests
- Physical measurements

Visit 7

Date/time: _____

- Bring diary cards, peak flow meter, and study drug
- Pregnancy test (*if applicable*)
- Blood draw
- Health history
- Questionnaires
- Breathing tests
- Physical measurements
- Exit interview

TRIM coordinator: _____
Coordinator phone: _____
After hours phone: _____