PROTOCOL: Improving Asthma Control in the Real World: A Systematic Approach to ImprovingDulera Adherence - a controlled study testing the effectiveness of an adult asthma adherence disease management program to improve asthma control by promoting adherence to Dulera

PROTOCOL VERSION DATE: January 6, 2014,Version1.0

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SOURCES OF SUPPORT: Asthma Management Systems (with an award from Merck)

1.0 Objective and Specific Aims

1) Enhance asthma control by delivering the asthma adherence disease management protoco,l *Asthma* AdherencePathway™.

2) Enhance adherence to Dulera relative to a clinical benchmark by delivering asthma adherence disease management protocol, *Asthma* Adherence Pathway™.

3) Initiate validation of Adult Asthma Adherence Questionnaire (AAAQ)

Hypotheses:

Primary Clinical Hypothesis: Poorly controlled subjects with moderate-to-severe asthma (measured by Asthma Control Questionnaire (ACQ) 1) despite treatment with Dulera, who are treated with the asthma adherence disease management protocol, *Asthma* Adherence Pathway™, will achieve greater asthma control than similar control subjects who are treated with thecurrent standard of care.

Primary end point: There will be four measures of Asthma Control Questionnaire (ACQ) over time over 3 months. The primary endpoint is the third month measure of ACQ.

Secondary Clinical Hypothesis: The asthma adherence disease management program, Asthma Adherence Pathway™, will increase observed adherence to Dulera relative to a benchmark of 60% adherence (i.e., expected prescribed actuations).

Secondary end points: a) Average adherence to Dulera over the three month study period

Tertiary Clinical Hypothesis: Responses to Adult Asthma Adherence Questionnaire (AAAQ) will be related to Dulera Adherence

Tertiary Study Endpoints: There will be 2 measures of the AAAQ (first and last visit) and the tertiary endpoint is the last visit

2.0 Background and Significance

Approximately 22 million Americans have asthma, 6 million under 18 years of a e.[1] The annual cost of asthma care is estimated at $19.7 billion,[2] with 456,000 hospitailzations and 1.5 million

ER visits.[2] African Americans are three times more likely to be hospitalized or die from asthma than other groups.[4] Inhaled corticosteroids effectively control symptoms and reduce morbidity, mortality, health care utilization and cost.[5] However, 45-60% of patients do not adhere to preventivedrug regimens.[6 7 8] Adherence rates for inhaled corticosteroids (ICS) range from 44% to 72%[7]. But only 8% to 13% of patients taking ICS continue to fill prescriptions after one year.[8]

It is difficult for clinicians to determine whether treatment failure is due to an inadequate medication regimen or poor adherence, in part because self-reported adherence is unreliable.[9] Physicians may get a false impression of a drug's effectiveness if a patient is not truthful about medication taken. Non-adherent patients are at risk for excess morbidity and mortality, as well as excess imaging, lab tests and consultations, due to the inability to accurately determine the cause of treatment failure.[10]

This study will assess adherence to the study medication, Dulera. This medication is being provided free of charge by Merck. Separate studies involving other asthma medications are warranted at a later time. The focus of this proposal is to test a treatment mode,l delivered by clinicians who acquire Adherence/Communicationskills, which may increase asthma control, improve adherence to Dulera, and enhance subjects' perception of the effectiveness of Dulera. The asthma adherence disease management (AADM) intervention strategy consists of three components: 1) objective adherence monitoring; 2) identificaiton of barriers to treatmen;t and 3) Motivational Interviewing adherence strategies that address specific barriers.[32] In an uncontrolled pilot study, the PI used medicaiton monitoring and psycho-educationaladherence programs in children with severe asthma to significantly reduce morbidity, ER use, hospitalization, and cost.[11] This research led to the formulation of AADM principles to be tested in this controlled study.[12] The research addresses two important knowledge gaps. First, NHLBI Expert Panel Report 3 (EPR-3) states that adherence monitoring is a key component of asthma management, but notes that the quality of the supporting data is weak, and encourages controlled trials to further evaluate the effectiveness of objective adherence monitoring.[13] Second, 56% of American Academy of Allergy Asthma & Immunology members responding to a survey, report that they lackcompetency managing non-adherent patients.[14]

Individual components of the model have been tested inp romot ing asthma adherence and improving control. Milgrom et al.[9] as well as Onyrimba et al.[1] demonstrated the effectiveness of using electronic adherence monitors attached to inhaled corticosteroid MDIs (ICS) to diagnose adherence status and improve adherence. Wilson et al demonstrated the effectiveness of shared-decision making, one type of patient-centered communication that has many features similar to Motivational Interviewing, to improve asthma control and adherence.[16] Weinsteinet al combined medicaiton monitoring with psycho-educationa family interventions to improve adherence and decrease morbidity and cost from asthma. The reduction in morbidity and cost was thought to be related to: objective feedback regarding medication use; identification of barriers and counseling that identified patienVfamily ambivalence about treatment; and enhancing motivationto follow thru with a complex treatment plan. Weinsteinemployed all three components of the model (ICS adherence monitors; assessment of adherence barriers; Motivational Interviewing adherence strategies) in reducing asthma costs by 72% in a pilot organized by Blue Cross Blue Shield DE.[17]

The rationale for using Motivational Interviewing is the observation that educating patients about asthma yields little improvement in adherence or outcomes.[18] Interventions that encourage patients to monitor symptoms or peak flow have shown significantbut small effects on asthma morbidity.[19] Self-management approaches, including identifying barriers to adherence, self-monitoring medicationuse, goal setting, and problem solving, result in fewer ER visits18, short-term improvements in adherence[19 20] higher asthma management self-efficacy,[20 21] improved

quality of life, [15,16] reduced asthma symptoms,[19,22] and less beta-agonist use.[19,22] Unfortunately, the majority of self-management studies involve more than 5.5 hours of patient contact.[23]

An important limitation of both educational and self-management approaches is that they are predicatedontheassumption that patients aremotivated to accept treatment recommendations. These approaches mi ht be effecitve for those who are ready to change but less so for those who are not ready.[24,2] Schmaling et al.[26] for example, found that asthma education resulted in increased knowledge but decreased motivation to use medication. There is a need for innovative approaches to promote motivation for medication adherence that 1) build on previously validated interventions, 2) are easily integrated into standard clinical care, and 3) target both those who are ready and those who are not ready to change.

Dr. Weinstein is a Motivational Interviewing trainer, with extensive experience in helping clinicians acquire adherence and communication skills. He designed and is the director of the Adherence and Communication Course held at the American Academy of Allergy Asthma & Immunology annual meeting, and has provided adherence/communication training to Allergy/Immunology training programs in the US. The use of patient-centered Motivational Interviewing Adherence Strategies (MIAS, reviewed below), as well as objective feedback on Dulera use, is expected to improve asthma control and improve adherence[2,7,28] Dr. Weinstein (in his role with the Asthma Management Systems) is the recipient of the Merck grant and a sponsor for this study. He is not a co-investigator for the study and will not make protocol decisions. He will provide training to the investigators and will be provided with a de-identified dataset for analysis.

Dr. Weinstein was part of a research team that developed a 5 question adherence questionnaire for adults with asthma (Adult Asthma Adherence Questionnaire-AAAQ).[33] The study of 420 subjects found that these 5 questions related to other measures of adherence and to asthma control can be used clinically to identify patients at risk of nonadherence and the specific adherence barriers involved.. Five items (Following my medication plan; forgetting; not needing ICS; side effects; and cost) were related to self-reported low adherence or previous ICS refill as well as asthma control (ACT). The AAAQ instrument will be used for the purposes of this research study.

3.0 Research Design and Methods

Study design:
This study will make use of a cluster experimental design where repeated assessments over time are nested within patients and patients are nested within physician. Some clinicians will be assigned to the treatment condition and some to the control group (which will be practicing the current standard of asthma care). A total of 60 subjects will be enrolled in to the study.

Subjects being seen for regular asthma care and who are beingprescribed Dulera 100/5 based upon asthma severity and dosing guidelines (and regardless of participation in this research study) will be asked to participate in this research study. Also, these subjects with asthma are routinelyprescribed Proventil HFA as their rescue inhaler. For the purposes of the study, these medications(Dulera 100/5 and Proventli HFA) will be provided to all subjects as part of study participation.

The subjects will be assigned to either the intervention or control group at the time they sign the consent form. These subjects will be placedinto their respective groups in an alternating

process, irrespective of subject demographics, treating clinician or previous asthma treatment to minimize bias

Study drug:
Dulera is a combination product containing a corticosteroid and a long-actingbeta2-adrenergic agonist, FDA approved and indicated for treatment of asthma in patients 12 years of age and older.

PROVENTIL® HFA Inhalation Aerosol is FDA approved and indicated in adults and children 4 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm. Proventil will be given as a rescue medication in this study.

Study drug will be kept at room-temperature in a locked cabinet located within Dr. Gentile's office and will be accessible only to study staff.

During the course of the study (after the screening), bothstudy drugs will include SmartInhaler adherence monitors. The SmartInhaler is FDA approved and will provide electronic data for recording and monitoring actuations of prescribed MDI usage. This electronic data will be downloaded to a password-protected computer at the study site.

Motivational interviewing:
Prior to the patient management phase, clinicians will receive training in asthma adherence disease management strategies as well as in Motivational Interviewing to optimize delivery of the adherence interventions. They will be given a written test regarding adherence/communicationprinciples prior to training and at the end of the study. The curriculum includes articles, video examples and role-playing. Asthma Management Systems LLC has developed and tested a web-based Asthma Adherence Disease Program *(Asthma* Adherence Pathway-SEE MEASURES BELOW) which guides patients and clinicians through the adherence interventions. (28) Patients identify adherence barriers from the *Asthma* Adherence Pathway. The patients receive written and video feedback regarding the significance oftheir concerns. This feedback previews potential strategies which will be delivered by clinician. The clinician reviews the barriers identified by the patient. He/she is presented with links to Motivational Interviewing Adherence Strategies, in both written and video formats. These strategies serve as prompts for interventions in the study by the clinician as a clinical decision support system. Weinstein will review this material at the training sessions and how to use it for subjects.

Measures (see a/so adherence flowchart below):

- ADHERENCE: Dulera adherence is calculated as the number of actuations measured by SmartInhaler divided by the number of actuations expected between clinic visits
    - Definition of Dulera Adherence: Subjects with 60% actuations during the interval between clinic visits
    - Definition of Dulera Nonadherence: Subjects with < 60% actuations during the interval between clinic visits (Rationale for 60% adherence cut-off is to maximize asthma control. 60% cut-off has been used by Ho and Bender et al (2006) as a suitable criterion of adherence).

- ASTHMA CONTROL QUESTIONNAIRE (ACQ):[29] [30] This brief questionnaire includes asthma symptoms, frequency of albuterol use and measureof pre-bronchodilator FEV-1,

providing 7 elements for analysis. There is a 1-6 likert scale for each item. The score is the mean of the 7 responses.

- WELL CONTROLLED: Scores 0.75
- NOT WELL CONTROLLED: Scores 1.5
- INDETERMINATE: Scores in between 0.76 and 1.49
  - For the INDETERMINATE group: asthma control will be determined by the frequency of Proventil HFA use.
    - "Well controlled" will be defined as the use of the Proventil HFA 2 inhalations 2 days per week during the interval not related to exercise
    - "Not well controlled" will be defined as the use of the Proventil HFA 2 inhalations 3 days per week during the interval not related to exercise

- *ASTHMA* ADHERENCE PATHWAY™ (completed by Intervention Group): The *Asthma* Adherence Pathway™ (AAP) is a computer-based Internet clinical decision support tool designed to improve adherence to medication and asthma management behaviors that affect asthma control. The subject completes the Internet-based AAP at entry into the study. This permits review by both subject and provider. The system recommends specific actions by the subject and provider based on the system's input. The subject inputs attitudes and behaviors about disease management at the entry of the study. The subject receives asthma and adherence education in both written and video format to reinforce subsequent interventions by the provider. Prior to onset of the study the provider receives training to implement the Motivational Interviewing Adherence Strategies (MIAS) that address the specific concerns of the subjects. The AAP provides the analysis of the subject's barriers in the form of "prompts" as a clinical decision making tool. It gives the provider recommendations on delivering MIAS that were presented in the earlier training. The adherence barriers identified by the subjects include (11):
  - Ineffective management: not following the asthma medication plan; delaying treatment of symptoms; not removing self from an area causing symptoms; not following instructions to treat an asthma attack; not measuring peak flow.
  - Negative attitudes about treatment: do not need medication; medicine does not work.
  - Symptoms during distressing emotional states: angry; upset; frustration; depression; anxiety.
  - Lack of comprehension of care instructions: uncertain when to use which medication; not understanding how to use prescribed medication, especially inhalation technique; not understanding how to use a peak flow meter.
  - Quality of life disruption: sleep, recreational activities, home activities, work, school.
  - Lack of agreement by significant other with the treatment plan
  - Cost, side effects, forgetfulness

  A 3-point likert scale (Never, Sometimes, Often) is provided for patients to identify barriers. Those responses (Never or Often) depending on the wording of the question that denote a "significant barrier" will be reviewed by the provider. The provider uses the recommended Motivational Interviewing Adherence Strategies contained within the software and presented in the training sessions. The Adult *Asthma* Adherence Pathway has been shown to have preliminary validation for non-adherent adults.[14]

- ADULT ASTHMA ADHERENCE QUESTIONNAIRE (AAAQ) (completed by Interventional Group): The AAAQ consists of five questions related to other measures of adherence and to asthma control that can be used clinically, to identify patients at risk of nonadherence and the specific adherence barriers involved. It uses a 6 likert scale. By comparing objectively measured adherence to the AAAQ, it would be possible to determine the validity of this brief instrument. Although only 20 subjects in the Intervention group will complete the AAAQ, the sponsor is conducting multiple adherence studies with the SmartInhaler that will provide sufficient numbers to evaluate the validity of the AAAQ.

VISIT PROCEDURES

Screening visit (all subjects) - approximately 2 hours:

- Subject completes consent form
- Subject given Dulera 100/5 and Proventil (without electronic SmartInhaler adherence monitors) and instructions for use
- Physical Examination and medical history
- Spirometry
- Subject completes asthma control questionnaire (ACQ)
- Study staff collects demographic information
- Demonstrate use of peak flow (subjects given diary to record and generate "personal best")

If subject experiences no side effects with Dulera 100/5 they will return in two weeks for a baseline visit (Week 2 ± 3 days) to be alternated between either the "Interventional" or "Control" (standard of care) group.

All subjects will continue to receive Dulera throughout the course of the study and this medication will be provided free of charge. All subjects will be provided with the Dulera medication guide and an individualized asthma action plan. Subjects will be informed of the potential of asthma symptoms and asked to contact the investigator for further instructions if they develop these symptoms.

INTERVENTIONAL GROUP

Baseline visit for Intervention group (Week 2 + 3 days) - approximately 60 minutes:

- Physical examination of upper/lower airways
- Assessment of adverse events, medications, and intercurrent illnesses
- Spirometry pre/post bronchodilator
- Subject completes asthma control questionnaire (ACQ)
- Subject completes Adult Asthma Adherence Questionnaire (AAAQ)
- Subject given Dulera 100/5 and Proventil (each with SmartInhaler device) and informed that it will measure MDI use and be reviewed at each visit.
- Evaluation (correction if needed) of inhalation technique of MDIs
- Subject completes asthma adherence disease management software *(Asthma* Adherence Pathway™) to identify patient barriers (5-10 minutes) and provide asthma education
- Clinician to initiate specific Motivational Interview Adherence Strategies as determined by AAP. If subject has more than 2 barriers, the clinician will review those at next clinic visit in 2 weeks.

- Revie w Peak flow diary and Asthma Action Plan with instructions to notify provider if Peak Flow :s: 50 % of measured peak flow during initial clinic visit. "Personal Best" to be identified at next clinic visit in 2 weeks.

Follow up visits for Intervention group - 60 minutes:

- Physical Examination
- Assessment of adverse events, medications, and intercurrent illnesses
- Spirometry without bronchodilator to determine ACQ
- Assessment and feedback of Dulera adherence
- Subject completes asthma control questionnaire(ACQ)
- Assessment of inhalation technique
- Review Peak Flow diary
- Subject and clinical interaction based upon adherence and asthma control measures (see adherence flowchart below)

Each time the patient is found to be nonadherent, he/she will be asked to return in 2 weeks ± 3 days for the next assessment (up to a maximum of 6 visits). A subject who is identified as non-adherent 3 times during the study will be asked to return for a final visit one month later and will not be given adherence feedback.

STANDARD OF CARE (CONTROL) GROUP

Baseline visit for Control group /Week 2 + 3 days} - approximatel y 60 minutes:

- Physica l examination of upper/lower airways
- Assessment of adverse events, medications, and intercurrent illnesses
- Spirometry pre- bronchodilator to determine ACQ
- Subject completes asthma control questionnaire (ACQ)
- Review Peak Flow diary and develop an Asthma Action Plan
- Provide Asthma Education

Follow up visits for Control group (Week 6, Week 10, Week 14, all ± 3 days) - approximatel y 60 minutes:

- Physica l examination of upper/lower airways
- Assessment of adverse events, medications, and intercurrent illnesses
- Spirometry pre- bronchodilatorto determine ACQ
- Subject completes asthma control questionnaire (ACQ)
- Review Peak Flow diary

Dose changes: It may be a possibility that during the course of this study, the research physician determines it is in the subject's best interest to increase the dose of Dulera to 200/5 based on the subject's asthma control and dosing guidelines. Any other changes in medication are discussed under Concomitant treatments.

Early Withdrawal of Subjects: Criter ia for subjec t withdra wal or rem oval from the study include the following:

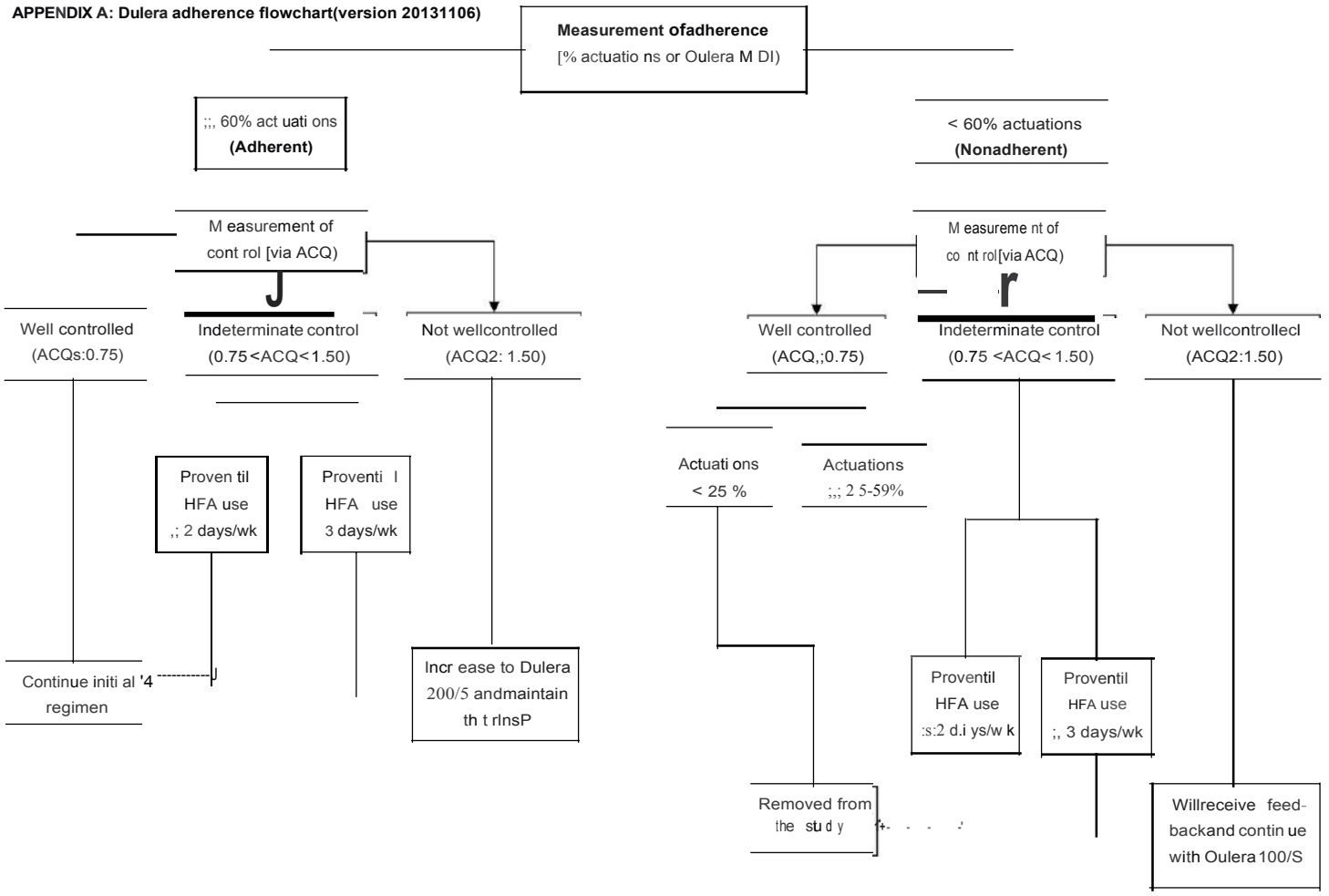
- untoward reaction to the study medications
- lost to follow up (do not report to the clinic for scheduled visit)

- non-compliance (do not return to the clinic with medication and monitors)
- subject consent withdrawal

Subjects who withdraw because of Dulera or Proventli side effects will receive follow-up phone calls within 24 hours to evaluate need for further follow-up care. All subjects who do not complete the protocol will be replaced.

Concomitant treatments: During the course of the study, the use of any other orally inhaled steroid formulations is prohibited, In addition, any medicaitons that are known to have a drug interaction with Dulera are prohibited. Any other medications are acceptable as long as dose remains stable over the course of the study. If it becomes necessary for the subject to begin one of these medications or change doses, they will be removed from the study and replaced.

APPENDIX A: Dulera adherence flowchart(version 20131106)



4.0 Statistical Considerations:

Statistical power: The ACQ consists of 7 questions scaled from 0 (best asthma control) to 6 (worst asthma control). Assuming a large treatment effect (i.e., a difference of .8 standard deviation units in the outcome) reflecting absolute change in the asthma control outcome, small-to-moderate levels of intraclass correlation, 40 patients nested within 8 clinicians in each condition, and alpha of .05, statistical power for the test of the primary hypothesis exceeds .80. The power analysis is based on a variance estimate of .70 and a score change of .5 in the ACQ being a minimal important difference.[31] The study plans to enroll up to 60 subjects as subjects who are non-compliant will be replaced to allow for 40 total to complete the study.

Planned statistical analysis: The primary analysis of the four repeated measures of the Asthma Control Questionnaire (ACQ) over time over 3 months will done using linear or nonlinear mixed modeling (Fitzmaurice, Laird, & Ware, 2011) to determine whether the intervention group demonstrates different average individual trajectories of change compared to the control group. The primary endpoint is the third month measure of the ACQ.

For the AAAQ secondary analysis, we will compare the observed versus expected ratios (mean or median depending on the distribution) in 1) patients with a positive (abnormal) response to question 1 (responses 2-6) versus those without a positive response (response 1); and 2) patients with a positive (abnormal) response to any question (QA: response 1-3; QB: response 1-4; QC: response 1-3; QD: response 1-3) versus those with no positive responses: QA: 4-6; QB:4-6; QC: 4-6; QD: 4-6. For the secondary analysis we will examine changes in the AAAQ over time (expressed as 0, 1, or 2 or more positive responses) in relationship to the change in observed versus expected ratios over time. The AAAQ will be completed at entry into the study and at the conclusion at 3 months. Suitable subjects in future studies that use electronic adherence monitors will also complete the AAAQ permitting an attempt to validate this instrument.

No interim statistical analysis will be done prior to compleiton of all data collection.

Missing data considerations: When dealing with missing data in a longitudinal study, restricting analyses to make use of only cases with complete repeatedly measured data can substantially bias statistical findings. Assuming data are missing at random (MAR) or missing completely at random (MCAR), multiple imputation and full information maximum likelihood estimation are two principled and recommended techniques for dealing with missingness. We will be using statistical packages (i.e., SAS, Mplus) that can accommodate missing data on the outcome variables and make use of all available data for each subject in planned analyses. As noted in the Research Design section earlier, we will include in statistical analysis all subjects who complete at least three clinical visits in either the intervention or control groups.

4.1 Inclusion of Children in Research: Subjects ages 18 and under will not be included in this study as this is a preliminary study and a separate, age-specific study in children is warranted in the future.

4.2 Inclusion/Exclusion Criteria:

Inclusion Criteria

1. Physician diagnosis of asthma of moderate severity
2. Subjects :2:: 18 years of age

3. Currently receiving an inhaled corticosteroid medication and being prescribed Dulera 100/5 as part of standard of care based upon asthma severity and dosing guidelines
4. Asthma Control Questionnaire (ACQ) result> 1.0 at entry
5. Demonstration of correct inhalation technique for use of meter-dosed inhalers (MDIs)
6. History of reversible airway obstruction documented by treating physician

Subjects will be recruited for intervention and control groups from the same geographic area and time of year to avoid seasonal variations of asthma symptoms and will be capable of giving informed consent.

Exclusion Criteria

1. Intermittent asthma (asthma exacerbations or symptoms< 3 days/week)
2. Diagnosis of emphysema in prior year
3. Diagnosis at any time of: chronic obstructive pulmonary disease (COPD), chronic bronchitis, cystic fibrosis, bronchiectasis, Churg Strauss, Wegener's, sarcoidosis, pulmonary hypertension or lung cancer
4. On any medicaiton documented to have a drug interaction with Dulera

4.3 Recruitment Procedures:
Subjects will be recruited from the investigator's patient practice population and referred by other physicians within the health system. Regardless of where subjects are recruited, consenting and all study visits and associated procedures will be performed in a private area in Dr. Gentile's practice.

Study investigators will obtain written informed consent from the subject before completing any study procedures Subjects will be given ample time to review the consent and all questions will be answered to ensure the subject's understanding.

4.4 Risk/Benefit Ratio:
This research study presents less than minimal risk to the subject in that the probability and magnitude of harm or discomfort anticipated are not greater in and of those ordinarily encountered in daily life or during routine physical exams or tests.

Risks of Du/era
The most common side effects of DULERA include inflammation of the nose and throat, inflammation of the sinuses, and headache. Less common side effects of Dulera include: serious allergic reactions, thrush (yeast infection) in the mouth and throat, a higher chance of infection, reduced adrenal function, increase in wheezing right after taking DULERA, lower bone mineral density, slowed growth in children, eye problems including glaucoma and cataracts, decrease in blood potassium and increase in blood sugar levels.

Formoterol, one of the active ingredients in DULERA, increases the risk of asthma-related death. In pediatric and adolescent patients, formoterol may increase the risk of asthma-related hospitalization. It has not yet been determined whether the use of inhaled corticosteroids (a component of DULERA) or other long-term asthma-control therapy decreases or eliminates this risk.

Risks of Proventil HFA
Risks of Proventil HFA include fast heart rate and high blood pressure, nausea, dizziness, nervousness, difficulty sleeping, headache, and a jittery or nervous feeling. These symptoms

usually go away within one hour. It is likely that subjects already use albuterol and are familiar with how they react to this medication.

Risks of questionnaires and interview procedures
An infrequent study risk includes fatigue and performance anxiety while completing questionnaires and interviews, or may cause discomfort if subject has a disagreement with the physician about medication use (adherence). Throughout the process, the subject will be queried about fatigue and adequate time will be allotted to allow the subject to rest. Open and honest dialogue with physician is encouraged, however subjects will not be required to answer any questions that make them uncomfortable.

Risks of Spirometry
Occasionally, spirometry may cause some dizziness, shortness of breath, cough or chest tightness. Subjects will be treated by a study doctor if these occur.

Risk of Unintentional Disclosure of your Private Health Informatio n
Another potential risk is an unintentional disclosure of private health information. However, this is very unlikely because the study team has procedures in place to try to prevent this from happening. The information collected will be stored in a locked office and on password protected computers.

Potential benefits
While there are no direct benefits from participation in the study, subjects may receive benefit from the study medication when taken, may experience improvement in their quality of life and may improve their medicaiton adherence for other treatments.

Proteciton Against Risk
All assessments will be completed by research staff and/or physicians trained in appropriate administration of assessment protocols or procedures Subjects will be instructed by investigators to avoid medications that have interactions with Dulera/Proventil. Subjects will also be instructed to discontinue medication if side effects develop.

Data Confidenitality and Integrity
The data collected will be used for research purposes only, and participants will be identified by code designation. All data collected for this project will be kept strictly confidential and will be kept in a locked cabinet or room. All data will be catalogued using the participant's study ID number. All research staff members are required to respect the confidentiality of participants and to complete institutionally required subject protection training.

Data and Safety Monitoring Plan
The principal investigator and study staff will review the study annually at the time of continuing review to assess adequacy of procedures and to ensure subject privacy, research confidentiality, data quality, and study procedures. Also to be assessed are study goals and modifications of those goals; subject recruitment, accrual and retention, progress in data coding and analysis, documentaiton, identificaiton of adverse events or research subject complaints, and any issues or concerns at that time. Also, assessment will be made of external factors or relevant information that may have an impact on the safety of study participants or the ethics of the research study.

5.0 Costs and Payments

5.1 Research Study Costs: Neither the participant, nor his/her insurance provider will be charged for the costs of any of the procedures performed for the purpose of this research study or for the Dulera and Proventil HFA study drug. The participant's health insurance will be billed in the standard manner for routine care costs. This includes any routine appointments with his/her physician(s) or any other tesUtherapies the doctor recommends. Any deductible or co-payments that are part of his/her insurance coverage will apply.

5.2 Research Study Payments:Participants will receive a $50 for each completed study visit, up to a maximum of $300 if all 6 visits are completed. Subjects will receive a Payoneer Debit MasterCard which can be used anywhere that debit MasterCards are accepted (including online). When subjects receive the card, they will be provided further information about the card including how to use the card, confidentiality, and privacy information. If a subjectreceives $600 or more from for taking part in this research study or a combination of studies in one tax year, they will be sent a 1099 form for tax purposes.

Study results and information may lead, in the future, to new inventions or products. If the research investigators are able to develop new products from the use of these study results or informaiton, there are currently no plans to share any money or other rewards that may result from the development of such a new product with the subjects.

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PROTOCOL: Improving Asthma Control in the Real World: A Systematic Approach to ImprovingDulera Adherence - a controlled study testing the effectiveness of an adult asthma adherence disease management program to improve asthma control by promoting adherence to Dulera

PROTOCOL VERSION DATE: January 6, 2014,Version1.0

PRINCIPAL INVESTIGATOR: Deborah Gentlie, MD, Allegheny Singer Research Institute. 490 East North Avenue, Suite 207, Pittsburgh, PA 15212

SOURCES OF SUPPORT: Asthma Management Systems (with an award from Merck)

1.0 Objective and Specific Aims

1) Enhance asthma control by delivering the asthma adherence disease management protoco,l *Asthma* AdherencePathway™.

2) Enhance adherence to Dulera relative to a clinical benchmark by delivering asthma adherence disease management protocol, *Asthma* Adherence Pathway™.

3) Initiate validation of Adult Asthma Adherence Questionnaire (AAAQ)

Hypotheses:

Primary Clinical Hypothesis: Poorly controlled subjects with moderate-to-severe asthma (measured by Asthma Control Questionnaire (ACQ) 1) despite treatment with Dulera, who are treated with the asthma adherence disease management protocol, *Asthma* Adherence Pathway™, will achieve greater asthma control than similar control subjects who are treated with thecurrent standard of care.

Primary end point: There will be four measures of Asthma Control Questionnaire (ACQ) over time over 3 months. The primary endpoint is the third month measure of ACQ.

Secondary Clinical Hypothesis: The asthma adherence disease management program, Asthma Adherence Pathway™, will increase observed adherence to Dulera relative to a benchmark of 60% adherence (i.e., expected prescribed actuations).

Secondary end points: a) Average adherence to Dulera over the three month study period

Tertiary Clinical Hypothesis: Responses to Adult Asthma Adherence Questionnaire (AAAQ) will be related to Dulera Adherence

Tertiary Study Endpoints: There will be 2 measures of the AAAQ (first and last visit) and the tertiary endpoint is the last visit

2.0 Background and Significance

Approximately 22 million Americans have asthma, 6 million under 18 years of a e.[1] The annual cost of asthma care is estimated at $19.7 billion,[2] with 456,000 hospitailzations and 1.5 million

ER visits.[2] African Americans are three times more likely to be hospitalized or die from asthma than other groups.[4] Inhaled corticosteroids effectively control symptoms and reduce morbidity, mortality, health care utilization and cost.[5] However, 45-60% of patients do not adhere to preventivedrug regimens.[6 7 8] Adherence rates for inhaled corticosteroids (ICS) range from 44% to 72%[7]. But only 8% to 13% of patients taking ICS continue to fill prescriptions after one year.[8]

It is difficult for clinicians to determine whether treatment failure is due to an inadequate medication regimen or poor adherence, in part because self-reported adherence is unreliable.[9] Physicians may get a false impression of a drug's effectiveness if a patient is not truthful about medication taken. Non-adherent patients are at risk for excess morbidity and mortality, as well as excess imaging, lab tests and consultations, due to the inability to accurately determine the cause of treatment failure.[10]

This study will assess adherence to the study medication, Dulera. This medication is being provided free of charge by Merck. Separate studies involving other asthma medications are warranted at a later time. The focus of this proposal is to test a treatment mode,l delivered by clinicians who acquire Adherence/Communicationskills, which may increase asthma control, improve adherence to Dulera, and enhance subjects' perception of the effectiveness of Dulera. The asthma adherence disease management (AADM) intervention strategy consists of three components: 1) objective adherence monitoring; 2) identificaiton of barriers to treatmen;t and 3) Motivational Interviewing adherence strategies that address specific barriers.[32] In an uncontrolled pilot study, the PI used medicaiton monitoring and psycho-educationaladherence programs in children with severe asthma to significantly reduce morbidity, ER use, hospitalization, and cost.[11] This research led to the formulation of AADM principles to be tested in this controlled study.[12] The research addresses two important knowledge gaps. First, NHLBI Expert Panel Report 3 (EPR-3) states that adherence monitoring is a key component of asthma management, but notes that the quality of the supporting data is weak, and encourages controlled trials to further evaluate the effectiveness of objective adherence monitoring.[13] Second, 56% of American Academy of Allergy Asthma & Immunology members responding to a survey, report that they lackcompetency managing non-adherent patients.[14]

Individual components of the model have been tested inp romot ing asthma adherence and improving control. Milgrom et al.[9] as well as Onyrimba et al.[1] demonstrated the effectiveness of using electronic adherence monitors attached to inhaled corticosteroid MDIs (ICS) to diagnose adherence status and improve adherence. Wilson et al demonstrated the effectiveness of shared-decision making, one type of patient-centered communication that has many features similar to Motivational Interviewing, to improve asthma control and adherence.[16] Weinsteinet al combined medicaiton monitoring with psycho-educationa family interventions to improve adherence and decrease morbidity and cost from asthma. The reduction in morbidity and cost was thought to be related to: objective feedback regarding medication use; identification of barriers and counseling that identified patienVfamily ambivalence about treatment; and enhancing motivationto follow thru with a complex treatment plan. Weinsteinemployed all three components of the model (ICS adherence monitors; assessment of adherence barriers; Motivational Interviewing adherence strategies) in reducing asthma costs by 72% in a pilot organized by Blue Cross Blue Shield DE.[17]

The rationale for using Motivational Interviewing is the observation that educating patients about asthma yields little improvement in adherence or outcomes.[18] Interventions that encourage patients to monitor symptoms or peak flow have shown significantbut small effects on asthma morbidity.[19] Self-management approaches, including identifying barriers to adherence, self-monitoring medicationuse, goal setting, and problem solving, result in fewer ER visits18, short-term improvements in adherence[19 20] higher asthma management self-efficacy,[20 21] improved

quality of life, [15,16] reduced asthma symptoms,[19,22] and less beta-agonist use.[19,22] Unfortunately, the majority of self-management studies involve more than 5.5 hours of patient contact.[23]

An important limitation of both educational and self-management approaches is that they are predicatedontheassumption that patients aremotivated to accept treatment recommendations. These approaches mi ht be effecitve for those who are ready to change but less so for those who are not ready.[24,2] Schmaling et al.[26] for example, found that asthma education resulted in increased knowledge but decreased motivation to use medication. There is a need for innovative approaches to promote motivation for medication adherence that 1) build on previously validated interventions, 2) are easily integrated into standard clinical care, and 3) target both those who are ready and those who are not ready to change.

Dr. Weinstein is a Motivational Interviewing trainer, with extensive experience in helping clinicians acquire adherence and communication skills. He designed and is the director of the Adherence and Communication Course held at the American Academy of Allergy Asthma & Immunology annual meeting, and has provided adherence/communication training to Allergy/Immunology training programs in the US. The use of patient-centered Motivational Interviewing Adherence Strategies (MIAS, reviewed below), as well as objective feedback on Dulera use, is expected to improve asthma control and improve adherence[2,7,28] Dr. Weinstein (in his role with the Asthma Management Systems) is the recipient of the Merck grant and a sponsor for this study. He is not a co-investigator for the study and will not make protocol decisions. He will provide training to the investigators and will be provided with a de-identified dataset for analysis.

Dr. Weinstein was part of a research team that developed a 5 question adherence questionnaire for adults with asthma (Adult Asthma Adherence Questionnaire-AAAQ).[33] The study of 420 subjects found that these 5 questions related to other measures of adherence and to asthma control can be used clinically to identify patients at risk of nonadherence and the specific adherence barriers involved.. Five items (Following my medication plan; forgetting; not needing ICS; side effects; and cost) were related to self-reported low adherence or previous ICS refill as well as asthma control (ACT). The AAAQ instrument will be used for the purposes of this research study.

3.0 Research Design and Methods

Study design:
This study will make use of a cluster experimental design where repeated assessments over time are nested within patients and patients are nested within physician. Some clinicians will be assigned to the treatment condition and some to the control group (which will be practicing the current standard of asthma care). A total of 60 subjects will be enrolled in to the study.

Subjects being seen for regular asthma care and who are beingprescribed Dulera 100/5 based upon asthma severity and dosing guidelines (and regardless of participation in this research study) will be asked to participate in this research study. Also, these subjects with asthma are routinelyprescribed Proventil HFA as their rescue inhaler. For the purposes of the study, these medications(Dulera 100/5 and Proventli HFA) will be provided to all subjects as part of study participation.

The subjects will be assigned to either the intervention or control group at the time they sign the consent form. These subjects will be placedinto their respective groups in an alternating

process, irrespective of subject demographics, treating clinician or previous asthma treatment to minimize bias

Study drug:
Dulera is a combination product containing a corticosteroid and a long-actingbeta2-adrenergic agonist, FDA approved and indicated for treatment of asthma in patients 12 years of age and older.

PROVENTIL® HFA Inhalation Aerosol is FDA approved and indicated in adults and children 4 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm. Proventil will be given as a rescue medication in this study.

Study drug will be kept at room-temperature in a locked cabinet located within Dr. Gentile's office and will be accessible only to study staff.

During the course of the study (after the screening), bothstudy drugs will include SmartInhaler adherence monitors. The SmartInhaler is FDA approved and will provide electronic data for recording and monitoring actuations of prescribed MDI usage. This electronic data will be downloaded to a password-protected computer at the study site.

Motivational interviewing:
Prior to the patient management phase, clinicians will receive training in asthma adherence disease management strategies as well as in Motivational Interviewing to optimize delivery of the adherence interventions. They will be given a written test regarding adherence/communicationprinciples prior to training and at the end of the study. The curriculum includes articles, video examples and role-playing. Asthma Management Systems LLC has developed and tested a web-based Asthma Adherence Disease Program *(Asthma* Adherence Pathway-SEE MEASURES BELOW) which guides patients and clinicians through the adherence interventions. (28) Patients identify adherence barriers from the *Asthma* Adherence Pathway. The patients receive written and video feedback regarding the significance oftheir concerns. This feedback previews potential strategies which will be delivered by clinician. The clinician reviews the barriers identified by the patient. He/she is presented with links to Motivational Interviewing Adherence Strategies, in both written and video formats. These strategies serve as prompts for interventions in the study by the clinician as a clinical decision support system. Weinstein will review this material at the training sessions and how to use it for subjects.

Measures (see a/so adherence flowchart below):

- ADHERENCE: Dulera adherence is calculated as the number of actuations measured by SmartInhaler divided by the number of actuations expected between clinic visits
    - Definition of Dulera Adherence: Subjects with 60% actuations during the interval between clinic visits
    - Definition of Dulera Nonadherence: Subjects with < 60% actuations during the interval between clinic visits (Rationale for 60% adherence cut-off is to maximize asthma control. 60% cut-off has been used by Ho and Bender et al (2006) as a suitable criterion of adherence).

- ASTHMA CONTROL QUESTIONNAIRE (ACQ):[29] [30] This brief questionnaire includes asthma symptoms, frequency of albuterol use and measureof pre-bronchodilator FEV-1,

providing 7 elements for analysis. There is a 1-6 likert scale for each item. The score is the mean of the 7 responses.

- WELL CONTROLLED: Scores 0.75
- NOT WELL CONTROLLED: Scores 1.5
- INDETERMINATE: Scores in between 0.76 and 1.49
  - For the INDETERMINATE group: asthma control will be determined by the frequency of Proventil HFA use.
    - "Well controlled" will be defined as the use of the Proventil HFA 2 inhalations 2 days per week during the interval not related to exercise
    - "Not well controlled" will be defined as the use of the Proventil HFA 2 inhalations 3 days per week during the interval not related to exercise

- *ASTHMA* ADHERENCE PATHWAY™ (completed by Intervention Group): The *Asthma* Adherence Pathway™ (AAP) is a computer-based Internet clinical decision support tool designed to improve adherence to medication and asthma management behaviors that affect asthma control. The subject completes the Internet-based AAP at entry into the study. This permits review by both subject and provider. The system recommends specific actions by the subject and provider based on the system's input. The subject inputs attitudes and behaviors about disease management at the entry of the study. The subject receives asthma and adherence education in both written and video format to reinforce subsequent interventions by the provider. Prior to onset of the study the provider receives training to implement the Motivational Interviewing Adherence Strategies (MIAS) that address the specific concerns of the subjects. The AAP provides the analysis of the subject's barriers in the form of "prompts" as a clinical decision making tool. It gives the provider recommendations on delivering MIAS that were presented in the earlier training. The adherence barriers identified by the subjects include (11):
  - Ineffective management: not following the asthma medication plan; delaying treatment of symptoms; not removing self from an area causing symptoms; not following instructions to treat an asthma attack; not measuring peak flow.
  - Negative attitudes about treatment: do not need medication; medicine does not work.
  - Symptoms during distressing emotional states: angry; upset; frustration; depression; anxiety.
  - Lack of comprehension of care instructions: uncertain when to use which medication; not understanding how to use prescribed medication, especially inhalation technique; not understanding how to use a peak flow meter.
  - Quality of life disruption: sleep, recreational activities, home activities, work, school.
  - Lack of agreement by significant other with the treatment plan
  - Cost, side effects, forgetfulness

  A 3-point likert scale (Never, Sometimes, Often) is provided for patients to identify barriers. Those responses (Never or Often) depending on the wording of the question that denote a "significant barrier" will be reviewed by the provider. The provider uses the recommended Motivational Interviewing Adherence Strategies contained within the software and presented in the training sessions. The Adult *Asthma* Adherence Pathway has been shown to have preliminary validation for non-adherent adults.[14]

- ADULT ASTHMA ADHERENCE QUESTIONNAIRE (AAAQ) (completed by Interventional Group): The AAAQ consists of five questions related to other measures of adherence and to asthma control that can be used clinically, to identify patients at risk of nonadherence and the specific adherence barriers involved. It uses a 6 likert scale. By comparing objectively measured adherence to the AAAQ, it would be possible to determine the validity of this brief instrument. Although only 20 subjects in the Intervention group will complete the AAAQ, the sponsor is conducting multiple adherence studies with the SmartInhaler that will provide sufficient numbers to evaluate the validity of the AAAQ.

VISIT PROCEDURES

Screening visit (all subjects) - approximately 2 hours:

- Subject completes consent form
- Subject given Dulera 100/5 and Proventil (without electronic SmartInhaler adherence monitors) and instructions for use
- Physical Examination and medical history
- Spirometry
- Subject completes asthma control questionnaire (ACQ)
- Study staff collects demographic information
- Demonstrate use of peak flow (subjects given diary to record and generate "personal best")

If subject experiences no side effects with Dulera 100/5 they will return in two weeks for a baseline visit (Week 2 ± 3 days) to be alternated between either the "Interventional" or "Control" (standard of care) group.

All subjects will continue to receive Dulera throughout the course of the study and this medication will be provided free of charge. All subjects will be provided with the Dulera medication guide and an individualized asthma action plan. Subjects will be informed of the potential of asthma symptoms and asked to contact the investigator for further instructions if they develop these symptoms.

INTERVENTIONAL GROUP

Baseline visit for Intervention group (Week 2 + 3 days) - approximately 60 minutes:

- Physical examination of upper/lower airways
- Assessment of adverse events, medications, and intercurrent illnesses
- Spirometry pre/post bronchodilator
- Subject completes asthma control questionnaire (ACQ)
- Subject completes Adult Asthma Adherence Questionnaire (AAAQ)
- Subject given Dulera 100/5 and Proventil (each with SmartInhaler device) and informed that it will measure MDI use and be reviewed at each visit.
- Evaluation (correction if needed) of inhalation technique of MDIs
- Subject completes asthma adherence disease management software *(Asthma* Adherence Pathway™) to identify patient barriers (5-10 minutes) and provide asthma education
- Clinician to initiate specific Motivational Interview Adherence Strategies as determined by AAP. If subject has more than 2 barriers, the clinician will review those at next clinic visit in 2 weeks.

- Revie w Peak flow diary and Asthma Action Plan with instructions to notify provider if Peak Flow :s: 50 % of measured peak flow during initial clinic visit. "Personal Best" to be identified at next clinic visit in 2 weeks.

Follow up visits for Intervention group - 60 minutes:

- Physical Examination
- Assessment of adverse events, medications, and intercurrent illnesses
- Spirometry without bronchodilator to determine ACQ
- Assessment and feedback of Dulera adherence
- Subject completes asthma control questionnaire(ACQ)
- Assessment of inhalation technique
- Review Peak Flow diary
- Subject and clinical interaction based upon adherence and asthma control measures (see adherence flowchart below)

Each time the patient is found to be nonadherent, he/she will be asked to return in 2 weeks ± 3 days for the next assessment (up to a maximum of 6 visits). A subject who is identified as non-adherent 3 times during the study will be asked to return for a final visit one month later and will not be given adherence feedback.

STANDARD OF CARE (CONTROL) GROUP

Baseline visit for Control group /Week 2 + 3 days} - approximatel y 60 minutes:

- Physica l examination of upper/lower airways
- Assessment of adverse events, medications, and intercurrent illnesses
- Spirometry pre- bronchodilator to determine ACQ
- Subject completes asthma control questionnaire (ACQ)
- Review Peak Flow diary and develop an Asthma Action Plan
- Provide Asthma Education

Follow up visits for Control group (Week 6, Week 10, Week 14, all ± 3 days) - approximatel y 60 minutes:

- Physica l examination of upper/lower airways
- Assessment of adverse events, medications, and intercurrent illnesses
- Spirometry pre- bronchodilatorto determine ACQ
- Subject completes asthma control questionnaire (ACQ)
- Review Peak Flow diary

Dose changes: It may be a possibility that during the course of this study, the research physician determines it is in the subject's best interest to increase the dose of Dulera to 200/5 based on the subject's asthma control and dosing guidelines. Any other changes in medication are discussed under Concomitant treatments.

Early Withdrawal of Subjects: Criter ia for subjec t withdra wal or rem oval from the study include the following:

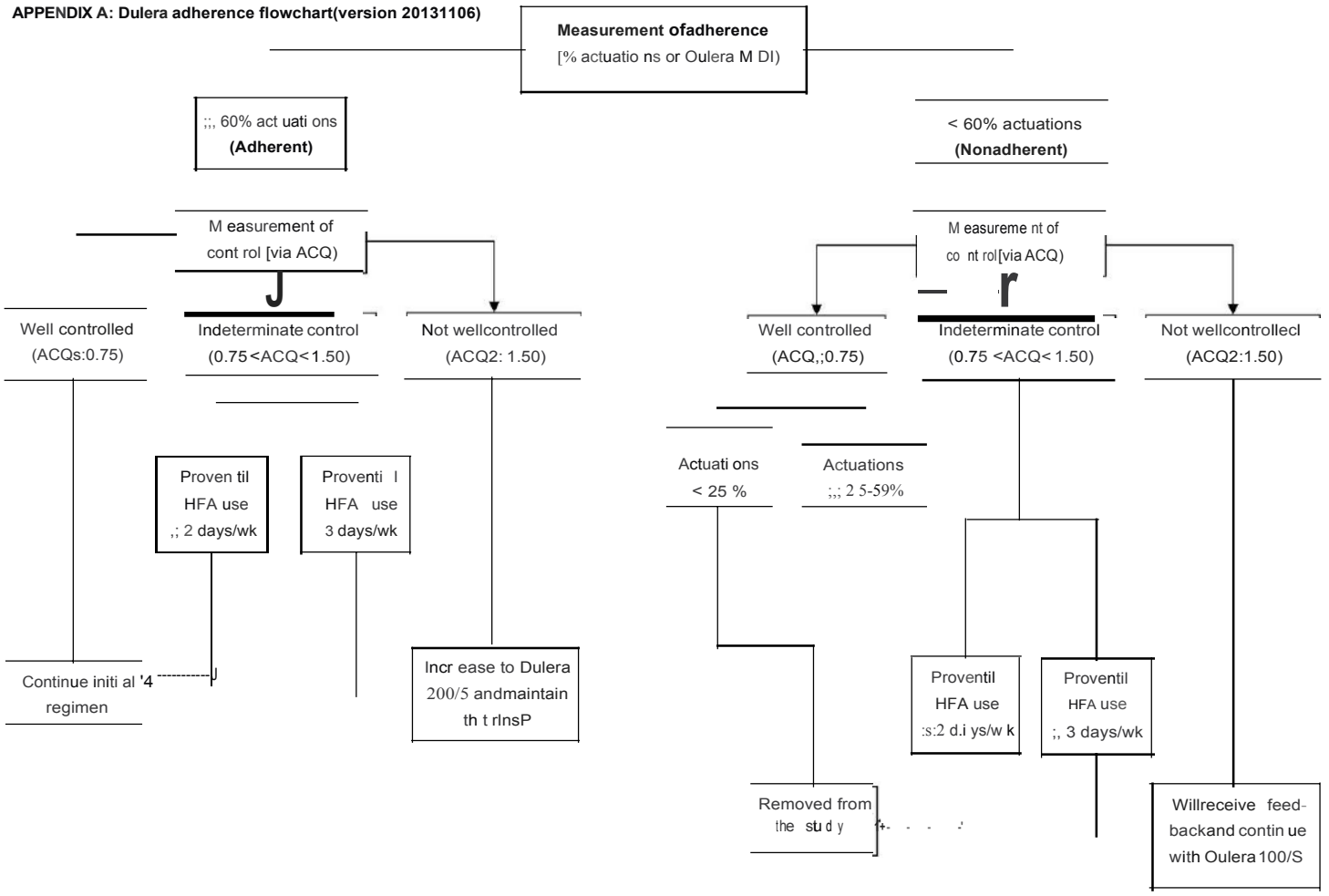
- untoward reaction to the study medications
- lost to follow up (do not report to the clinic for scheduled visit)

- non-compliance (do not return to the clinic with medication and monitors)
- subject consent withdrawal

Subjects who withdraw because of Dulera or Proventli side effects will receive follow-up phone calls within 24 hours to evaluate need for further follow-up care. All subjects who do not complete the protocol will be replaced.

Concomitant treatments: During the course of the study, the use of any other orally inhaled steroid formulations is prohibited, In addition, any medicaitons that are known to have a drug interaction with Dulera are prohibited. Any other medications are acceptable as long as dose remains stable over the course of the study. If it becomes necessary for the subject to begin one of these medications or change doses, they will be removed from the study and replaced.

APPENDIX A: Dulera adherence flowchart(version 20131106)



4.0 Statistical Considerations:

Statistical power: The ACQ consists of 7 questions scaled from 0 (best asthma control) to 6 (worst asthma control). Assuming a large treatment effect (i.e., a difference of .8 standard deviation units in the outcome) reflecting absolute change in the asthma control outcome, small-to-moderate levels of intraclass correlation, 40 patients nested within 8 clinicians in each condition, and alpha of .05, statistical power for the test of the primary hypothesis exceeds .80. The power analysis is based on a variance estimate of .70 and a score change of .5 in the ACQ being a minimal important difference.[31] The study plans to enroll up to 60 subjects as subjects who are non-compliant will be replaced to allow for 40 total to complete the study.

Planned statistical analysis: The primary analysis of the four repeated measures of the Asthma Control Questionnaire (ACQ) over time over 3 months will done using linear or nonlinear mixed modeling (Fitzmaurice, Laird, & Ware, 2011) to determine whether the intervention group demonstrates different average individual trajectories of change compared to the control group. The primary endpoint is the third month measure of the ACQ.

For the AAAQ secondary analysis, we will compare the observed versus expected ratios (mean or median depending on the distribution) in 1) patients with a positive (abnormal) response to question 1 (responses 2-6) versus those without a positive response (response 1); and 2) patients with a positive (abnormal) response to any question (QA: response 1-3; QB: response 1-4; QC: response 1-3; QD: response 1-3) versus those with no positive responses: QA: 4-6; QB:4-6; QC: 4-6; QD: 4-6. For the secondary analysis we will examine changes in the AAAQ over time (expressed as 0, 1, or 2 or more positive responses) in relationship to the change in observed versus expected ratios over time. The AAAQ will be completed at entry into the study and at the conclusion at 3 months. Suitable subjects in future studies that use electronic adherence monitors will also complete the AAAQ permitting an attempt to validate this instrument.

No interim statistical analysis will be done prior to compleiton of all data collection.

Missing data considerations: When dealing with missing data in a longitudinal study, restricting analyses to make use of only cases with complete repeatedly measured data can substantially bias statistical findings. Assuming data are missing at random (MAR) or missing completely at random (MCAR), multiple imputation and full information maximum likelihood estimation are two principled and recommended techniques for dealing with missingness. We will be using statistical packages (i.e., SAS, Mplus) that can accommodate missing data on the outcome variables and make use of all available data for each subject in planned analyses. As noted in the Research Design section earlier, we will include in statistical analysis all subjects who complete at least three clinical visits in either the intervention or control groups.

4.1 Inclusion of Children in Research: Subjects ages 18 and under will not be included in this study as this is a preliminary study and a separate, age-specific study in children is warranted in the future.

4.2 Inclusion/Exclusion Criteria:

Inclusion Criteria

1. Physician diagnosis of asthma of moderate severity
2. Subjects :2:: 18 years of age

3. Currently receiving an inhaled corticosteroid medication and being prescribed Dulera 100/5 as part of standard of care based upon asthma severity and dosing guidelines
4. Asthma Control Questionnaire (ACQ) result> 1.0 at entry
5. Demonstration of correct inhalation technique for use of meter-dosed inhalers (MDIs)
6. History of reversible airway obstruction documented by treating physician

Subjects will be recruited for intervention and control groups from the same geographic area and time of year to avoid seasonal variations of asthma symptoms and will be capable of giving informed consent.

Exclusion Criteria

1. Intermittent asthma (asthma exacerbations or symptoms< 3 days/week)
2. Diagnosis of emphysema in prior year
3. Diagnosis at any time of: chronic obstructive pulmonary disease (COPD), chronic bronchitis, cystic fibrosis, bronchiectasis, Churg Strauss, Wegener's, sarcoidosis, pulmonary hypertension or lung cancer
4. On any medicaiton documented to have a drug interaction with Dulera

4.3 Recruitment Procedures:
Subjects will be recruited from the investigator's patient practice population and referred by other physicians within the health system. Regardless of where subjects are recruited, consenting and all study visits and associated procedures will be performed in a private area in Dr. Gentile's practice.

Study investigators will obtain written informed consent from the subject before completing any study procedures Subjects will be given ample time to review the consent and all questions will be answered to ensure the subject's understanding.

4.4 Risk/Benefit Ratio:
This research study presents less than minimal risk to the subject in that the probability and magnitude of harm or discomfort anticipated are not greater in and of those ordinarily encountered in daily life or during routine physical exams or tests.

Risks of Du/era
The most common side effects of DULERA include inflammation of the nose and throat, inflammation of the sinuses, and headache. Less common side effects of Dulera include: serious allergic reactions, thrush (yeast infection) in the mouth and throat, a higher chance of infection, reduced adrenal function, increase in wheezing right after taking DULERA, lower bone mineral density, slowed growth in children, eye problems including glaucoma and cataracts, decrease in blood potassium and increase in blood sugar levels.

Formoterol, one of the active ingredients in DULERA, increases the risk of asthma-related death. In pediatric and adolescent patients, formoterol may increase the risk of asthma-related hospitalization. It has not yet been determined whether the use of inhaled corticosteroids (a component of DULERA) or other long-term asthma-control therapy decreases or eliminates this risk.

Risks of Proventil HFA
Risks of Proventil HFA include fast heart rate and high blood pressure, nausea, dizziness, nervousness, difficulty sleeping, headache, and a jittery or nervous feeling. These symptoms

usually go away within one hour. It is likely that subjects already use albuterol and are familiar with how they react to this medication.

Risks of questionnaires and interview procedures
An infrequent study risk includes fatigue and performance anxiety while completing questionnaires and interviews, or may cause discomfort if subject has a disagreement with the physician about medication use (adherence). Throughout the process, the subject will be queried about fatigue and adequate time will be allotted to allow the subject to rest. Open and honest dialogue with physician is encouraged, however subjects will not be required to answer any questions that make them uncomfortable.

Risks of Spirometry
Occasionally, spirometry may cause some dizziness, shortness of breath, cough or chest tightness. Subjects will be treated by a study doctor if these occur.

Risk of Unintentional Disclosure of your Private Health Informatio n
Another potential risk is an unintentional disclosure of private health information. However, this is very unlikely because the study team has procedures in place to try to prevent this from happening. The information collected will be stored in a locked office and on password protected computers.

Potential benefits
While there are no direct benefits from participation in the study, subjects may receive benefit from the study medication when taken, may experience improvement in their quality of life and may improve their medicaiton adherence for other treatments.

Proteciton Against Risk
All assessments will be completed by research staff and/or physicians trained in appropriate administration of assessment protocols or procedures Subjects will be instructed by investigators to avoid medications that have interactions with Dulera/Proventil. Subjects will also be instructed to discontinue medication if side effects develop.

Data Confidenitality and Integrity
The data collected will be used for research purposes only, and participants will be identified by code designation. All data collected for this project will be kept strictly confidential and will be kept in a locked cabinet or room. All data will be catalogued using the participant's study ID number. All research staff members are required to respect the confidentiality of participants and to complete institutionally required subject protection training.

Data and Safety Monitoring Plan
The principal investigator and study staff will review the study annually at the time of continuing review to assess adequacy of procedures and to ensure subject privacy, research confidentiality, data quality, and study procedures. Also to be assessed are study goals and modifications of those goals; subject recruitment, accrual and retention, progress in data coding and analysis, documentaiton, identificaiton of adverse events or research subject complaints, and any issues or concerns at that time. Also, assessment will be made of external factors or relevant information that may have an impact on the safety of study participants or the ethics of the research study.

5.0 Costs and Payments

5.1 Research Study Costs: Neither the participant, nor his/her insurance provider will be charged for the costs of any of the procedures performed for the purpose of this research study or for the Dulera and Proventil HFA study drug. The participant's health insurance will be billed in the standard manner for routine care costs. This includes any routine appointments with his/her physician(s) or any other tesUtherapies the doctor recommends. Any deductible or co-payments that are part of his/her insurance coverage will apply.

5.2 Research Study Payments:Participants will receive a $50 for each completed study visit, up to a maximum of $300 if all 6 visits are completed. Subjects will receive a Payoneer Debit MasterCard which can be used anywhere that debit MasterCards are accepted (including online). When subjects receive the card, they will be provided further information about the card including how to use the card, confidentiality, and privacy information. If a subjectreceives $600 or more from for taking part in this research study or a combination of studies in one tax year, they will be sent a 1099 form for tax purposes.

Study results and information may lead, in the future, to new inventions or products. If the research investigators are able to develop new products from the use of these study results or informaiton, there are currently no plans to share any money or other rewards that may result from the development of such a new product with the subjects.

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