Determining Optimal Dose of Corticosteroids in COPD Exacerbations: A Pilot Study

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STUDY INFORMATION

Title of Project: Determining Optimal Dose of Corticosteroids in COPD Exacerbations: A Pilot Study

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1.0 Research Introduction

1.1 Purpose/Specific Aims

The goal of the study is to determine whether a high-dose corticosteroid regimen in patients admitted to the hospital with COPD exacerbations is associated with better clinical outcomes and at acceptable risk of adverse effects compared to a low-dose corticosteroid regimen. The study population includes patients ≥ 40 years-old with a ≥ 10 pack-years smoking history and a diagnosis of COPD, emphysema, or chronic bronchitis who present to the emergency room with increased dyspnea, increased sputum, or increased cough that requires admission to the hospital. We will perform a prospective, randomized, double-blinded study to determine if a high-dose corticosteroid regimen, which is already in use in clinical practice, decreases treatment failure compared to a low-dose corticosteroid regimen that is based on national consensus guidelines.

A. Objectives

Primary Aim: To determine if a high-dose corticosteroid regimen is associated with decreased rates of treatment failure compared to a low-dose corticosteroid regimen.

Secondary Aims:
a) To determine if a high-dose corticosteroid regimen is associated with a reduced length of stay.
b) To determine if a high-dose corticosteroid regimen is associated with better quality of life scores.

Tertiary Aim: To determine if a high-dose corticosteroid regimen is associated with an increased risk of short-term adverse effects.

B. Hypotheses / Research Question(s)

Our hypothesis is that high-dose corticosteroids are associated with a decreased rate of treatment failure, shorter length of hospital stay, and improved quality of life with similar risk of adverse effects.

1.2 Research Significance

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease that is characterized by progressive airflow limitation that is not fully reversible. The airflow limitation is associated with an abnormal inflammatory response of the lung to noxious particles or gases, such as cigarette smoke.[1]

Patients with COPD may come into the hospital with frequent acute exacerbations or flares of their disease, especially as the severity of their COPD increases.[3] These acute exacerbations of COPD contribute significantly to morbidity and worsen quality of life.[3] In patients with moderate to severe COPD, the in-hospital mortality rate was 9.9% with a 1-year mortality rate of 24.4% among those who were able to be discharged home.[5]

Oral or intravenous corticosteroids are recommended as an addition to other therapies in the management of COPD exacerbations.[1, 6-9] A 2008 Cochrane review confirms that there is a significant reduction in the risk of treatment failure and rate of relapse within a month of treatment with corticosteroids. In the steroid treated group, the length of hospital stay was also significantly reduced with an increased rate of improvement in lung function and dyspnea.[9] The FEV1 measured after bronchodilation increased by 90 mL daily up to day 5 of the hospital stay.[6]

While corticosteroids are required in the treatment of COPD exacerbations, the dose and duration of this treatment is still unclear and remains to be defined. Current consensus guidelines on the dose and duration of corticosteroid treatment vary. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends 30-40 mg of oral prednisolone daily for 7-10 days.[1] The Canadian Thoracic Society recommends oral or intravenous 25-50 mg of prednisone equivalent per day for 14 days; however, shorter treatment periods of between 7 and 14 days may also be effective.[10] In the UK, the National Institute for Health and Clinical Excellence (NICE) recommends prednisolone 30 mg orally for 7-14 days; although, their consensus guidelines also state, “there is still debate about the optimal dose and duration.”[11]

Various studies have evaluated the route of administration, dose, and duration of corticosteroid treatment in COPD exacerbations. De Jong compared oral to intravenous administration of the same dose of prednisolone for 5 days and found no significant difference in treatment failure, length of hospital stay, or changes in spirometry and quality of life.[12] A large cohort study evaluated different doses and found that oral low-dose steroids (prednisone 20-80 mg daily) were associated with a decreased risk of treatment failure and length of stay compared to intravenous high-dose therapy (120-800 mg prednisone equivalent daily).[13] A VA Cooperative study compared placebo to a 2-week and an 8-week corticosteroid taper. Rates of treatment failure were significantly higher in the placebo group than in the two glucocorticoid groups, but the 8-week regimen was not superior to the 2-week one.[7] The

effectiveness of shorter corticosteroid regimens has been studied. A 10-day course of steroid treatment was more effective than a 3-day course in improving PaO_2, FVC and FEV_1, and symptom scores for dyspnea on exertion.[14] Additionally, the REDUCE trial demonstrated non-inferiority of a 5-day regimen of prednisone 40mg daily when compared to an extended 14-day course.[15]

This research protocol will help further delineate the optimal dose of corticosteroids when given over a 10-day period consistent with prior research.

1.3 Research Design and Methods

We will perform a pilot study evaluating two commonly used doses of corticosteroids in the treatment of acute exacerbation of COPD. The study design is a randomized, double-blinded, prospective interventional trial. Our research staff will recruit, consent, and enroll patients admitted to the hospital with a diagnosis of COPD exacerbation. We will create randomization tables that will be provided to the research pharmacist. The research pharmacist will be telephoned, and they will randomly assign the patient to a low-dose or high-dose corticosteroid regimen. Medication will be prepared by a research pharmacist to maintain blinding. For in-hospital intravenous medication, the research pharmacist will provide to the nurses a container with the patient's name and medication without the dose. For oral medication, the pills will be inserted into a capsule and provided to nurses for in-hospital administration. At the time of discharge, a container filled with the remaining oral medication will be provided to the patient. Subjects receiving intravenous corticosteroid may be discharged to a nursing home before completion of the IV component of the regimen. Their regimen will be converted to oral equivalents, and a container will be provided to the nursing home. Copies of the patient brochure, signed consent, and written discharge instructions will also be provided. All data will be collected by our research staff via chart review of index and subsequent hospitalizations within the 30-day follow up period, as well as a phone interview with the patient at 30-days. The Clinical COPD Questionnaire will be administered during the phone interview. A patient is considered lost to follow-up if the data collection is not collected within 14 days after the 30-day follow-up date. In the event that we are unable to contact the patient, we will telephone the participant's personal medical doctor to confirm the patient's status. If necessary, we will obtain medical records for any outpatient physician visits made during the 30-day follow up period.

i. Primary Outcome: The composite of treatment failure defined as death, intubation, re-admission for COPD exacerbation, or intensification of therapy (increased steroid use, change of antibiotic therapy) within a 30-day follow-up period.

ii. Secondary Outcomes: Length of hospital stay and quality of life measured by Clinical COPD Questionnaire. The CCQ consists of 10 questions about the severity of COPD symptoms and limitation of activities over the prior week.

iii. Tertiary Outcome: Composite outcome of short-term adverse effects. Defined as hyperglycemia, hypertension, adrenal suppression, psychiatric disturbance, infection, and gastrointestinal bleed that require a consultation, an invasive procedure, or initiation of a specific therapy.

Subject participation in the study ends after the 30 day follow up period. Study staff will also maintain contact with the patient's hospital physician and actively review the patient's chart during the index hospitalization for safety and adverse effect monitoring. Please see the study data collection form for additional specific data points that will be collected.

1.4 Preliminary Data

No relevant preliminary data exists in our study. Interim analysis will not be performed on the data because of the relatively small sample size of this pilot study.

1.5 Sample Size Justification

This is a pilot study of 125 subjects to determine the rates of the outcomes so an adequate sample size can be determined and feasibility established. We do not anticipate including enough patients to have adequate power to definitively answer the hypothesis.

1.6 Study Variables

A. Independent Variables, Interventions, or Predictor Variables

Our independent variable is the corticosteroid intervention. We chose to compare two commonly used corticosteroid regimens for COPD exacerbation that vary by dosage strength but not duration. Both of these regimens may be considered "standard of care."

B. Dependent Variables or Outcome Measures

i. Primary Outcome: The composite of treatment failure defined as death, intubation, re-admission for COPD exacerbation, or intensification of therapy (increased steroid use, change of antibiotic therapy) within a 30-day follow-up period.
ii. Secondary Outcomes: Length of hospital stay and quality of life measured by Clinical COPD Questionnaire. The CCQ consists of 10 questions about the severity of COPD symptoms and limitation of activities over the prior week.
iii. Tertiary Outcome: Composite outcome of short-term adverse effects. Defined as hyperglycemia, hypertension, adrenal suppression, psychiatric disturbance, infection, and gastrointestinal bleed that require a consultation, an invasive procedure, or initiation of a specific therapy.

1.7 Drugs/Devices/Biologics

We chose to compare two commonly used corticosteroid regimens for COPD exacerbations, both of which might be considered "standard of care." All corticosteroids will be prepared, stored, and dispensed at the RWJUH main pharmacy by the staff research pharmacist.

i. Low dose arm: Methylprednisolone 10 mg IV q8hrs for 3 days*, then prednisone 40 mg PO daily for 4 days, then prednisone 30 mg daily for 1 day, then prednisone 20 mg daily for 1 day, then prednisone 10 mg daily x 1 day, then stop.

   * If the patient is unable to receive IV medications, every three consecutive doses of methylprednisolone will be replaced with a single dose of prednisone 40 mg PO given daily.

ii. High dose arm: Methylprednisolone 40 mg IV q8hrs for 3 days*, then prednisone 80 mg PO daily for 4 days, then prednisone 60 mg daily for 1 day, then prednisone 40 mg daily for 1 day, then prednisone 20 mg daily for 1 day, then stop.

   * If the patient is unable to receive IV medications, every three consecutive doses of methylprednisolone will be replaced with a single dose of prednisone 80 mg PO given daily.

If patients in either group are discharged prior to day 4, IV methylprednisolone will be converted to PO as above.

1.8 Primary Specimen Collection

N/A

1.9 Interviews, Focus Groups, or Surveys

A. Administration

The Clinical COPD Questionnaire (CCQ) will be administered by research staff during a telephone interview at 30 days following subject enrollment into the study. The patient will be provided this document in advance, at the time of hospital discharge, for reference.

B. Study Instruments

The CCQ is a validated tool utilized in prior literature to assess quality of life in patients with COPD. Higher scores indicate increased severity of symptoms and/or poorer quality of life, and are associated with increased mortality. [17, 18, 19, 20, 21]

In addition to the CCQ, research staff will query the patient about study endpoints during the follow-up telephone interview (re-admission, changes to steroid regimen, antibiotic therapy, and steroid-associated adverse effects that require a consultation, an invasive procedure, or initiation of a specific therapy).

1.10 Timetable/Schedule of Events

Patients will be enrolled and followed for a total of 30 days. If follow-up is still unable to be obtained 14 days after the 30-day follow-up date, the patient will be considered lost to follow-up. The global timetable for the study is unknown, as the volume of patient recruitment is unclear.

2.0 Project Management

2.1 Research Staff and Qualifications

Jeffrey L Carson, MD, the study Principal Investigator, is the Provost-New Brunswick, Rutgers Biomedical Health Sciences, Professor of Medicine Rutgers, Robert Wood Johnson Medical School. Dr Carson has extensive experience in leading and conducting randomized clinical trials including the NIH funded Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) trial, which enrolled patients from 47 centers from the United States and Canada. He is currently the Study Chairman and Principal Investigator of the NIH funded Myocardial Ischemia and Transfusion (MINT) trial, which will enroll 3500 patients from over 50 centers in the United States and Canada.

James Prister, MD is the Associate Program Director of the Internal Medicine Residency Program Rutgers Robert Wood Johnson Medical School and an attending physician Robert Wood Johnson University Hospital. Dr Prister is the study co-Investigator who is directly responsible for the ongoing conduct of the study.

Helaine Noveck, MPH is a research teaching specialist in the Division of General Internal Medicine, Department of Medicine, Rutgers Robert Wood Johnson Medical School. Ms Noveck was the Deputy Director of the Clinical Coordinating Center for FOCUS and currently serves in that role for MINT. She is experienced in both data management and analysis, having worked on Dr Carson's research projects for the past 24 years. Ms Noveck will serve as the data analyst.

2.2 Resources Available

The study will utilize locked file cabinets and a password protected workstation in the GIM office, CAB suite 2300. Ms Noveck will keep the key for the file cabinet.

All research co-investigators undergo initial two-hour training sessions regarding study protocol, procedures, and duties. On-going research procedures are supervised by James Prister and the data analyst to ensure protocol compliance.

2.3 Research Sites

Robert Wood Johnson University Hospital

3.0 Multi-Site Research Communication & Coordination

N/A

3.1 Outside Research

N/A

4.0 Research Data Source/s

4.1 Primary Data-Subjects and Specimens

Thirty day follow is obtained from patient/proxy via telephone contact (see data collection form).

4.2 Subject Selection and Enrollment Considerations

A. Recruitment Details

Emergency room and medical staff will be informed about the study objectives, eligibility criteria, and protocol requirements prior to the initiation of the study. We will only recruit patients of physicians who are willing to follow the study protocol. Study staff will be notified of potential subjects that are identified by the emergency room staff and physicians. Study staff can also access a list of patients in the hospital who are being treated with prednisone or methylprednisolone to identify additional potential study subjects. Study staff will assess the medical records of each of the potential study subjects and, if they meet all eligibility criteria, approach the patient for consent. Eligible patients would have a diagnosis of COPD, emphysema, or chronic bronchitis with a presentation of increased dyspnea, increased sputum, or increased cough.

B. Source of Subjects

Subjects will be recruited from the RWJUH emergency room and general medical ward.

C. Method to Identify Potential Subjects

See section A above.

D. Subject Screening

Individuals will be screened for study inclusion by study staff using the eligibility and screening form.

- **Inclusion Criteria**
  - Patients with a diagnosis of COPD, emphysema, or chronic bronchitis
  - Age ≥ 40 years-old
  - Smoking history ≥ 10 pack-years
  - Presentation to the emergency room with increased dyspnea, increased sputum, or increased cough
  - Admission to the hospital
- **Exclusion Criteria**
  - Alternative diagnosis for cause of dyspnea, increased sputum or cough
  - Patients who require intubation at time of recruitment
  - Patients who are unable to give consent
  - Patients who are pregnant or could be pregnant or are currently breast-feeding

- Women of child-bearing age who cannot use methods of contraception as described in the consent, including condoms, female condoms, cervical caps, diaphragms, and IUDs.
- Patients who were previously entered into the trial and are re-admitted to the hospital with a new COPD exacerbation.

A younger population is excluded because COPD is primarily an adult disease.

E. Recruitment Materials

Subjects will be given a copy of the informed consent as well as a short patient brochure describing the salient points of the study.

F. Lead Site Recruitment Methods

N/A

4.3 Subject Randomization

At the time of recruitment, subjects are assigned a consecutively numbered patient identifier by the study staff. This patient identifier is communicated to the research pharmacy. The research pharmacy then assigns a separate randomization identifier based on a previously computer generated randomization chart. The randomization identifier is communicated back to the study staff. This randomization identifier is associated with a specific treatment arm (low-dose or high-dose) on the randomization chart. The treatment arm associated with the randomization identifier **is not communicated** to the research staff because this is a double-blinded study. Study drug is prepared by the research pharmacy based on the assigned treatment arm.

4.4 Secondary Subjects

N/A

4.5 Number of Subjects

A. Total Number of Subjects: 125
B. Total Number of Subjects If Multicenter Study: N/A
C. Require Number of Subjects to Complete Research: This is a pilot study and our goal is to recruit as close to 125 subjects as possible.
D. Feasibility Of Recruiting: COPD exacerbation is a common reason for inpatient admission, however recruiting may be limited to unquantifiable external factors (ie. patient interest, physician participation, etc.).

4.6 Consent Procedures

A. Consent

- **Documenting Consent**

Informed consent will be obtained directly from the participant using study informed consent. If the patient agrees to participate in the trial, the signed IRB approved consent form will be placed in the subject's study file and the recruiter will keep make a copy to be placed in the patient's medical record and a copy to provide to the participant.

- **Waiver of Documentation Of Consent**

N/A, all consent will be documented.

- **Waiver or Alteration of Consent Process**

N/A

B. Consent Process

- **Location of Consent Process**

Consent will take place in the patient's hospital room.

- **Ongoing Consent**

The patient will be spoken with daily by the study staff while hospitalized to address any patient concerns regarding ongoing consent and potential adverse effects.

- **Individual Roles for Researchers Involved in Consent**

1. Consent Discussion Duration
The consent discussion is expected to take an average of 15-30 minutes depending on the level of subject understanding.
2. Coercion or Undue Influence
Vulnerable subjects that are unable to give consent or do not adequately understand the study are excluded from recruitment. Aside from paid-for trial medication, the study does not incentivize subject participation in any way, minimizing undue influence on indigent populations.
3. Subject Understanding
After the study is explained to the subjects, study staff will administer the Evaluation to Sign Consent which will document the subject's understanding of the study protocol. Only who provide acceptable responses to the Evaluation to Sign Consent will be enrolled.

4.7 Special Consent/Populations

A. Minors-Subjects Who Are Not Yet Adults

- **Criteria for Consent of Minors**

N/A

- **Wards of the State**

N/A

1. Research in NJ Involving Minors

N/A

2. Research Outside of NJ Involving Minors

N/A

- **Parental Permission**

N/A

- **Non-Parental Permission**

N/A

- **Assent Process**

N/A

1. Documentation of Assent

N/A

- **Non-English Speaking Subjects**

Non-English speakers will not be recruited

1. Process for Non-English Speaking Subjects

N/A

- **Short Form Consent for Non-English Speakers**

No one will be enrolled using the short form consent

B. Adults Unable to Consent / Cognitively Impaired Adults (*for interventional studies*)

- **NJ Law-Assessment of Regaining the Capacity To Consent**

N/A, subjects unable to give consent are excluded from this study.

- **Capacity To Consent**

N/A

- **NJ Law-Selecting A Witness**

N/A

- **Removing a Subject**

N/A

4.8 Economic Burden and/or Compensation for Subjects

A. Expenses

Subjects will not incur any additional expenses as a result of study participation.

B. Compensation/Incentives

Subjects will not be incentivized in any way for participation in the study, with the exception that trial medication will be provided at no cost to the subjects.

4.9 Risks to Subjects

A. Description of Subject Risk

Patients entered into this study would have received corticosteroids regardless of study participation. The optimal dose of corticosteroids in the treatment of COPD exacerbations in patients admitted to the hospital is unknown. The proposed regimen for the low-dose

corticosteroid group is based on national consensus guidelines, and the regimen for the high-dose group, on current clinical practices. Thus, the risks to subjects from study participation are comparable to current standard of care. Any patient who does not clinically improve appropriately can have their regimen intensified based on the clinical judgement of his/her physician. Additionally, if the treating physician feels that the patient is experiencing undue adverse effects from study corticosteroid, the patient may be withdrawn from the study at any time. Minor side effects (ie. hyperglycemia) from short-term systemic corticosteroids are common and generally limited in duration to the duration of treatment. They are an accepted consequence of the standard of care for COPD exacerbation. Major adverse effects are uncommon.

B. Procedures for Risks to Embryo, Fetus, and/or Pregnant Subjects
N/A, these subjects are excluded from the study.

C. Risks to Non-Subjects
N/A

D. Assessment of Social Behavior Considerations
Temporary psychiatric symptoms or exacerbation of pre-existing psychiatric disease are uncommon but potential side effects of corticosteroid therapy. The duration of these side effects are limited to the duration of corticosteroid therapy. Patients entered into this study would have received corticosteroids regardless of study participation. Thus, study participation is unlikely to increase risk of these side effects.

- **Reasonably Foreseeable Risks**
  There are no other reasonably foreseeable social behavior risks of participation in this study.
- **Risk Of Imposing An Intervention On Subject With Existing Condition**
  See above.
- **Other Foreseeable Risks**
  N/A
- **Observation And Sensitive Information**
  N/A

E. Minimizing Risks
Strict measures are in place to ensure patient confidentiality. Direct patient identifiers (names, addresses, and telephone numbers) will be collected on a separate form from the clinical data and will be kept in a locked file cabinet in the Department of General Internal Medicine, CAB suite 2300. The identifiers will never be entered into an electronic database. Subjects will be given a sequential study identification number that will be used on all forms that collect clinical data and in the electronic database.

The treatment regimens being compared are commonly used in current clinical care and would have been prescribed for the patients regardless of study participation. If the patient's

symptoms are not adequately relieved by the study medication, the treating physician is permitted to administer supplemental steroid as needed.

Patients will be followed while in the hospital (for up to 30 days) and at 30 days following study entry. All serious adverse events that have occurred will be identified and reported to the Institutional Review Board.

Any subject deaths will be reported within 24 hours of identification. Serious events will be defined as any event that is life threatening requires or prolongs hospitalization, produces a disability, results in a congenital anomaly/birth defect, or other conditions which in the judgment of the investigators represent significant hazards. All serious adverse events will be reported within one week of identification. All unexpected events meeting will be reported within two weeks of identification if they meet the following criteria:

Unexpected: not identified in nature, severity or frequency in the current IRB-approved research protocol, the informed consent document, the package insert for a given drug or the investigator's brochure.

Associated with the study intervention: there is a reasonable possibility that the event may have been caused by the research intervention.

F. Certificate of Confidentiality
N/A
G. Potential Benefits to Subjects
There is no direct benefit to study participants.
H. Provisions to Protect the Privacy Interests of Subjects
Subjects will interact with a limited number of study staff, primarily during the initial recruitment/inpatient follow-up period. Any privacy interests will be honored by study staff.

I. Research Team Access To Subject Data
Study participants will be asked to sign a Release of Medical Record form, allowing the research team to access medical information from all subsequent hospitalizations and outpatient physician visits within the 30-day follow up period.

4.10 Secondary Data – Records/Chart Reviews/Databases/Tissue Banks/etc.

4.11 Chart/Record Review Selection
For the index hospitalization, study staff will review the hospital medical record (paper and electronic) at the time of discharge for each outcome. The electronic record system is Sunrise Clinical Manager. Paper data collection forms that contain personal identifiers and health information will be kept locked in a

filing cabinet in the Department of General Internal Medicine, CAB suite 2300. Study variables and outcomes will be entered into an electronic database using identification numbers for the study subjects. With the exception of dates, the database will not contain personal identifiers. Only study staff will have access to the paper data collection forms and electronic database. In addition, all electronic data will be password-protected and stored on a HIPAA compliant university computer in the Department of General Internal Medicine. Please see the Data Collection Form for variables that will be collected/analyzed. Any forms linking collected data with patient identifiers will be destroyed at the completion of the study (2 years following termination of patient enrollment).

4.12 Secondary Specimen Collection

N/A

5.0 Special Considerations

5.1 Health Insurance Portability and Accountability Act (HIPAA)

HIPAA data (patient identifiers) will be collected as part of the data collection process. This data will not be disclosed and all patient identifiers will be destroyed at the completion of the study following data analysis. Authorization for study staff to obtain/analyze HIPAA data is included in the consent form.

5.2 Family Educational Rights and Privacy Act (FERPA)

N/A

5.3 NJ Access to Medical Research Act

N/A

5.4 Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)

A. "Special" Classes Of Subjects

(1) *Pregnant Women:* N/A, these subjects are excluded from the study.

(2) *Neonates:* N/A, these subjects are excluded from the study.

(3) *Neonates of Uncertain Viability:* N/A, these subjects are excluded from the study.

(4) *Prisoners:* N/A, these subjects are excluded from the study.

(5) *Children:* N/A, these subjects are excluded from the study.

(6) *Cognitively Impaired Adults:* N/A, these subjects are excluded from the study.

6.0 Research Data Protection and Reporting

6.1 Data Management and Confidentiality

A. Descriptive statistics (e.g., means, standard deviations, ranges, frequency distributions) will be examined for all relevant measures, and transformations of measures will be considered on the bases of distribution diagnostics and outlier analysis. The baseline characteristics of the patients in each of the two arms of the trial will be described and compared using chi-square statistics for categorical variables and t-tests or Wilcoxon statistics for continuous variables.

The intention-to-treat principle will be used for all randomized comparisons of study outcomes. The event rates for the primary, secondary, and tertiary clinical outcomes will be compared according to assigned corticosteroid group using chi-square statistics. The test for differences between groups in the composite primary outcome will be conducted at an alpha level of 0.05. The event rates for the individual clinical events and the additional pre-specified clinical events will be tested by treatment group with an alpha=0.01 to adjust for multiple comparisons. Event rates, absolute differences, and relative risks will be estimated, and 95% confidence intervals will be calculated.

B. This is a pilot study to establish an adequate sample size for a larger scale study as well as baseline event rates, thus a power analysis is not included in this submission.

C. Paper data will be stored in a locked filing cabinet in the Department of General Internal Medicine. A password-protected electronic database (that does not contain patient identifiers) will be stored on a HIPAA-compliant university computer at the same location. Helaine Noveck will have sole access to this data until the study enters the data analysis phase. All study personnel are already trained in HIPAA procedures and have signed HIPAA confidentiality agreements as part of obtaining access to the Sunrise Clinical Manager system.

D. Collected data will be reviewed for quality and internal consistency by study staff after initial collection and before the data analysis phase of the study.

E. Data to be collected includes patient identifiers and can be found in the data collection form. This data will be stored on paper and in an electronic database as detailed above. Paper data will be transported by research staff involved in patient recruitment/data collection to the central data repository at the General Internal Medicine office. Patient identifying data will be stored for 2 years following termination of patient enrollment (completion of the study), at which point all patient identifiers will be permanently destroyed. De-identified data will be retained indefinitely for future research purposes. All co-investigators will potentially have access to research data for data analysis/quality control purposes. Access to the data is controlled by the study data analyst, who maintains the central repository of paper/electronic data.

6.2 Data Security

Paper data collection forms that contain personal identifiers and health information will be kept locked in a filing cabinet in the Department of General Internal Medicine. Study variables and outcomes will be entered into an electronic database using identification numbers for the study subjects. With the exception of dates, the database will not contain personal identifiers. Only study staff will have access to the paper data collection forms and electronic database. In addition, all electronic data will be password-protected and stored on a HIPAA compliant university computer in the Department of General Internal Medicine. Any forms linking collected data with patient identifiers will be destroyed at the completion of the study (2 years following termination of patient enrollment).

6.3 Data and Safety Monitoring

A. Periodic Data Evaluation

Study staff responsible for data collection will review that data for potential corticosteroid adverse effects / unexpected patient outcomes and report problems to Helaine Noveck, James Prister, and Jeff Carson. Study policies involving adverse effect / death reporting to the IRB are in place and detailed above.

B. Type of Data Evaluated

Data reviewed includes predefined corticosteroid adverse effects in the data collection form and unexpected patient outcomes discovered by study staff.

C. Collection of Safety Information

Safety information is collected by study staff interviewing the patient and reviewing their chart while hospitalized, as well as phone interview and final chart review of index hospitalization and subsequent healthcare encounters at 30-day follow up.

D. Frequency Of Data Collection

Safety information is collected daily while the subject is hospitalized, starting at the point of patient recruitment. It is collected once more at the 30-day subject follow up.

E. Reviewer of Data

Study staff (co-investigators) responsible for patient recruitment/data collection/patient follow up will conduct an initial review of the data. Potential problems are reported to Helaine Noveck, James Prister, and Jeff Carson who will provide secondary review.

F. Schedule Of Review Of Cumulative Data

Cumulative data is not reviewed in this study, as it is a pilot study with a small sample size and is not powered to attain statistical significance for secondary safety outcomes.

G. Tests for Safety Data

N/A, see section F above.

H. Suspension of Research

Research will be immediately suspended if a serious, unexpected adverse effect is reported that is reasonably thought to be a direct result of the study drug and is thought to pose a risk to other study subjects beyond that of receiving standard-of-care doses of corticosteroids.

6.4 Reporting Results

A. Sharing of Results with Subjects

Results will not be shared with study subjects since no data is collected that is not ordered by the patient's treating physician.

B. Individual Results

N/A, see section A above.

C. Aggregate Results

Aggregate results will not be available for an extended period of time following study completion and will not be shared on an individual basis with study subjects. The study results will be published in a scientific journal for public consumption.

D. Professional Reporting

The study results will be published in a scientific journal for public consumption.

E. ClinicalTrials.Gov Registration And Data Reporting

The study is registered on ClinicalTrials.gov.

7.0 Data and/or Specimen Banking

N/A

8.0 Other Approvals/Authorizations

N/A

9.0 Bibliography

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