Suppressive Antibacterial Therapy with Once-weekly Solosec®(secnidazole) Oral Granules to Prevent Recurrent Bacterial Vaginosis

Drug Name: Solosec®(secnidazole) Oral Granules, 2 g

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STUDY PROTOCOL

Suppressive Antibacterial Therapy with Once-Weekly Secnidazole Granules to Prevent Recurrent Bacterial Vaginosis; a Pilot Study

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1. Background & Rationale

Forty to fifty percent of women with vaginal complaints will be diagnosed with bacterial vaginosis (BV) making it the most prevalent cause of vaginal symptoms in women nationally. Greater than 50% of women will have a repeat episode of BV within 1 year of standard treatment. [1] Recurrent BV, defined as three or more symptomatic episodes within 1 year, may be associated with multiple treatment failures over periods of several years or months. While there are no universally agreed upon treatment protocols for recurrent BV, the current CDC referenced treatment regimens include a 14-day course of metronidazole or tinidazole followed by twice-weekly or daily nitroimidazole therapy for up to six months.[2]

Secnidazole is a nitroimidazole antimicrobial indicated for the treatment of bacterial vaginosis in adult women with a much longer half-life than both metronidazole and tinidazole. While suppressive therapy can be curative or can increase symptom free intervals, patient compliance with complicated and prolonged treatment regimens are barriers to successful outcomes. Compared to metronidazole and tinidazole, secnidazole has a much longer half-life (metronidazole and tinidazole: 8 hours and 12-14 hours vs. secnidazole: 17-29 hours).

To date, there are no studies that have evaluated secnidazole for suppressive therapy of recurrent BV. In a randomized double-blind trial, clinical cure and/or symptom improvement rates were similar in women with bacterial vaginosis treated with a single dose of secnidazole (90.8%) or tinidazole (87.5%). Data from two non-blinded studies indicated that a single dose of secnidazole was at least as effective as 7-day treatment with metronidazole (secnidazole 73.3 to 93.1%; metronidazole 58.5 to 95.8%). [3]

From this data, it is reasonable to speculate that once weekly dosing of secnidazole for suppressive therapy of recurrent BV may be at least as effective as the current more complex therapies and would be a valuable treatment alternative to women suffering with recurrent BV due to the more simplified dosing regimen.

Simplifying suppressive protocols could improve patient compliance and decrease the recurrence of disease. Poor adherence increases with longer durations of treatment and studies of compliance rates show that 50% of women do not adhere to 5-7 day treatments for BV.[4,5] Poor adherence leads to treatment failures and recurring infections and increases the potential for resistant organisms.[6] Utilizing a drug such as secnidazole, which has a much longer half-life may provide an improved therapeutic window for suppression of causative microorganisms and could prevent a recurrence.

2. Objectives

2.1 Primary Objective. To determine the efficacy and safety of once-weekly oral secnidazole granules for suppressive therapy of recurrent BV to previously published efficacy and safety data of multiple-dose nitroimidazole suppressive regimens for the treatment of recurrent BV.

2.2 Secondary Objective. To determine the meantime to recurrence of BV after treatment.

2.3 Tertiary/Exploratory/Correlative Objectives. To evaluate participant compliance, tolerance, and occurrence of adverse events.

3. Outcome Measures/Endpoints

3.1 Primary Outcome Measures To estimate the efficacy and safety of once-weekly oral secnidazole granules for suppressive therapy of recurrent BV and to qualitatively compare to previously published efficacy and safety data of multiple-dose nitroimidazole suppressive regimens for the treatment of recurrent BV to aid in the design of a larger comparative trial.

3.1.1 Efficacy: The primary efficacy endpoint is failed treatment, defined as having at least 1 episode of RBV in the 30 week follow-up period. An episode of RBV (failed treatment) will be diagnosed if the subject has a Amsel score of 3 or higher. We will report total number of RBV episodes, overall failure rate, and time to failure after initial treatment. We will also report rates of RBV if diagnosed as >=1 Amsel criteria is met per FDA recommendations, but the primary outcome will be >=2 criteria to be consistent with prior literature and recommendations.

3.1.2

3.1.2.1 The Amsel criteria:

3.1.2.1.1 Thin, white, yellow, homogeneous discharge

3.1.2.1.2 Clue cells on wet mount microscopy

3.1.2.1.3 a vaginal fluid pH of over 4.5 when placing the discharge on litmus paper

3.1.2.1.4 Release of fishy odor when adding 10% potassium hydroxide (KOH) solution to wet mount - also known as "whiff test."

3.1.3 Safety: adverse events via MedDRA criteria.

3.2 Secondary Outcome Measures Time to recurrence measured by failure rates and time-to-failure. Defined by Amsel's criteria or by Nugent criteria (gram stain results). To be measured at visit 2 (3-5 days after initial treatment), visits 3-6 (week 6, 10, 14, and 18 during suppressive treatment), visits 7 & 8 (22 & 30 weeks after initiation of treatment).

3.3 Tertiary/Exploratory/Correlative Outcome Measures Participant compliance, tolerance, and adverse event data to be collected via a patient questionnaire at each visit. The safety of secnidazole was evaluated in five Phase 1 clinical trials before FDA approval. The five most common treatment-associated adverse events were: vulvovaginal candidiasis, headache, nausea, diarrhea, abdominal pain, and vulvovaginal pruritis. We will monitor for the frequency and severity of these events and any other subject-related side effects.

4. Eligibility Criteria

4.1 Inclusion Criteria

- Age 18 -50
- Ability to consent in English
- Current symptomatic bacterial vaginosis infection ($\geq$ 3 Amsel criteria).
  - Amsel's criteria: Homogenous vaginal discharge, vaginal pH >4.5, positive amine odor, and/or presence of >20% clue cells /hpf on saline mount microscopy
- History of at least 2 previous episodes of BV in the past 1 year.

Continuation after Second Visit

- Clinical resolution of bacterial vaginosis defined as: (asymptomatic and $\leq$ 2 Amsel criteria, will also be reported as asymptomatic and $\leq$ 1 Amsel criteria).

4.2 Exclusion Criteria

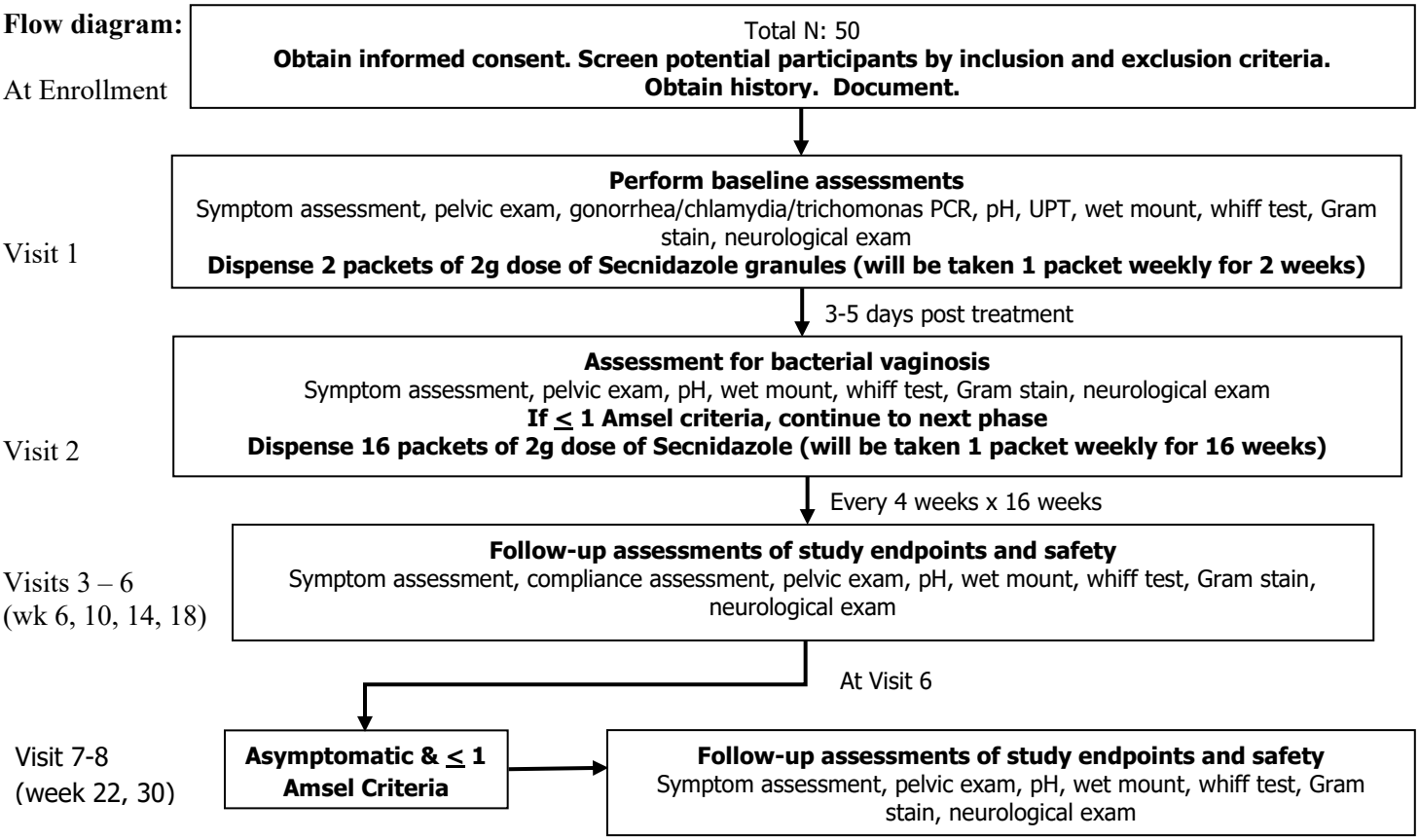
- Current gynecologic infection or condition, including candida vaginitis, gonorrhea, chlamydia, trichomonas, desquamative inflammatory vaginitis, atrophic vaginitis.
- Pre-existing heart conditions
- Pre-existing neurological conditions
- Currently Pregnant or breastfeeding
- Women taking anticoagulants, lithium, metoclopramide, or disulfiram therapy
- Hypersensitivity to secnidazole or other drugs in the same class.

5. Study Design

A single-center prospective pilot study with once-weekly oral secnidazole granule treatment of an acute condition for two weeks followed by prophylactic treatment of asymptomatic responders with once-weekly secnidazole for 16 weeks, followed by no therapy for 12 weeks. The final follow-up evaluation is at week 30.

Eligible women with a current symptomatic bacterial vaginosis infection ($\geq$ 3 Amsel criteria) and a history of at least 2 previous episodes of bacterial vaginosis in the past year will be enrolled in the open-label treatment study. All women will be treated with 2g of secnidazole granules orally once weekly for 2 weeks. At the second visit, 3-5 days after completion of treatment, women who have a clinical resolution of bacterial vaginosis (asymptomatic and $\leq$2 Amsel criteria, will also be reported as asymptomatic and < 1 Amsel criteria) will continue on once-weekly secnidazole for 16 weeks.

Patients will be evaluated at week 6, 10, 14, and 18 for recurrence of bacterial vaginosis. This will include questions about symptoms as well as a pelvic examination for assessment of vaginal discharge ($\geq$ 3 Amsel criteria). We will also collect any information on other clinical evaluations for recurrence and the dates of diagnoses and types of treatments they may have received. Those who remain without recurrence during the 16-week suppressive phase will be followed for an additional 12 weeks off therapy, with assessment for recurrence at weeks 22 and 30. Throughout the study, data will be collected on participants' compliance and on the occurrence of adverse events.



6. Enrollment

Participants presenting to the IU Coleman Center with a history of recurrent bacterial vaginosis who are currently symptomatic will be evaluated for enrollment in the study. Informed consent will be obtained.

7. Study Procedures

At each visit where women are evaluated for BV they will be asked about vaginal discharge. Then they will undergo a speculum examination of the vagina similar to pelvic examinations performed clinically at most annual gynecologic examinations. Any vaginal discharge present will be collected by a swab for assessment of pH, odor, and presence of clue cells on microscopy. The speculum examination should take ~2 minutes.

At the initial enrollment visit, subjects will be given a point-of-care pregnancy test. If the test is positive, the subject will not be placed on study drug, and will receive alternate, traditional suppressive therapy. Women enrolled will be instructed in the use of the secnidazole granules by trained study personnel or the medical provider. If a subject becomes pregnant during the study, we will terminate study drug for the subject and follow the subject for any adverse pregnancy outcomes for safety reporting. The subject will have a basic neurological test at enrollment.

At follow up visits, women will again be queried about vaginal discharge and will undergo a speculum examination as above, even if they do not endorse vaginal discharge. Subject will have a basic neurological test at follow up visits.

Women will be asked about any adverse side effects of the secnidazole including vaginal irritation, bleeding, redness, or itching. If the subject presents with vulvovaginal candidiasis, they will be treated with oral or vaginal fluconazole, per patient preference, if they present to the PI, or with the standard of care if they present elsewhere. The treatment will be noted.

If the subject or potential subject has any history of heart disease or disorders of the heart, they will be excluded from participation.

If a study participant has recurrence of bacterial vaginosis while on protocol, the subject will fail study treatment, and will be placed on alternate, traditional suppressive therapy. The participant will have completed the study at this point.

8. Study Calendar

	Treatment						Follow Up		Unscheduled
Event/Procedure	Enrollment/V1 Day 1	V2 Day 18	V3 Week 6	V4 Week 10	V5 Week 14	V6 Week 18	V7 Week 22	V8 Week 30	Unscheduled
Window		+/- 1 day	+/- 5 days	+/- 5 days	+/- 5 days	+/- 5 days	+/- 5 days	+/- 5 days	
Screening	x								
Confirm eligibility	x								
Informed consent	x								
Collection of MHx	x								
Symptom Assessment	x	x	x	x	x	x	x	x	x
Pelvic Exam	x	x	x	x	x	x	x	x	Per SOC
STI Testing	SOC								Per SOC
Whiff test	x	x	x	x	x	x	x	x	Per SOC
Vaginal pH	x	x	x	x	x	x	x	x	Per SOC
Wet mount	x	x	x	x	x	x	x	x	Per SOC
Gram stain	x	x	x	X	x	x	x	x	Per SOC
Study Drug Administration	x	X*	X*	X*	X*	X*			
Med compliance assessment			x	x	x	x			

**study drug provided to asymptomatic subjects only at V2 - V6.*

9. Reportable Events

The study is expected to be only slightly greater than minimal risk as the study medications and examinations are those that are commonly used during routine clinical care and evaluations. Secnidazole (study drug) has FDA approval for the treatment of acute BV with minimal side effects reported.

Any severe adverse effects including unexpected hospitalization due to treatment will be reported per IRB guidelines. Any non-severe Adverse Events ("AE"s) such as sensitivity or side effects will be reported in aggregate at annual reviews. Expected/common side effects of the examinations are discomfort and irritation. There is a minimal risk of vaginal bleeding. Side effects reported with secnidazole include vulvovaginal candidiasis, headache, mild gastrointestinal discomfort, and vaginal itching.

An adverse event ("AE") is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug-related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding that is unrelated to the intent of the study), symptom, or disease temporally associated with the use of a drug. An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.
Pre-existing conditions are not considered adverse events unless there is an unexpected change in the frequency, intensity, or nature of the condition. A newly diagnosed pregnancy during study enrollment will not be considered an adverse event. If a pregnancy occurs during the treatment or maintenance phases of the study, the subject will be asked to discontinue the study drug and be terminated from the study.

Pregnancy reports:
Pregnancy reports of subjects should be forwarded to Lupin Research Inc. This also includes normal pregnancies without AE. If a pregnancy occurs during the treatment or maintenance phases of the study, the subject will be asked to discontinue study drug and be terminated from the study.
The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and presence or absence of any birth defect, congenital abnormalities or maternal and newborn complications. Pregnancy follow-up should be conducted until the outcome.

The pregnancy reporting procedure should be the same as the Serious AE reporting procedure set out in Section 2.7 of the Agreement.

Additional Notes on Adverse Events and Serious Adverse Events:
For the purposes of this study, changes in clinical criteria (i.e. Amsel criteria and/or symptoms) from baseline that are associated with BV will be captured on the corresponding case report forms and should not be recorded as an adverse event with the following exception:

- If in the investigator/clinician's opinion a subject treated for BV gets a secondary infection (e.g. yeast infection), the yeast infection should be captured as an adverse event.

Each AE or suspected adverse reaction must be assessed for its seriousness. The term "serious" is not synonymous with "severe" that may be used to describe the intensity of an event or reaction. An AE or suspected adverse reaction is considered serious if in the view of either the investigator:

- Results in death
- Is life threatening (referring to an adverse event or suspected adverse reaction in which either the investigator or the sponsor believes the subject was at risk of death at the time of the event or reaction; it does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in a persistent or significant disability/incapacity
- Is considered medically important

Important medical events are those that may not be immediately life threatening but are of major clinical significance and may require intervention to prevent one of the other serious outcomes listed above. Examples include a seizure that did not require in-subject hospitalization or allergic bronchospasm that needed emergency treatment.

All adverse events or suspected adverse reactions that do not meet the criteria for serious will be regarded as non-serious.
Definition of Unexpectedness: An adverse event or suspected adverse reaction is considered unexpected if the nature/specificity or severity of the event or reaction is not consistent with applicable product information.
Documentation of Adverse Events: All adverse events (serious and non-serious) that occur from the time informed consent is signed through Visit 8 must be reported and recorded in source documentation and the appropriate page(s) of te CRF. Information to be documented for each AE includes the following:

- Adverse event term
- Severity of the event (mild, moderate, or severe)
- Start and stop date (if applicable)
- Time of the event if it occurred on the first day of study drug administration
- Relationship to study drug (none, possible, probable, definite)
- Action taken with the study drug (none, study drug interrupted, study drug discontinued)
- Action taken (none, new medication/treatment, termination from study, hospitalization, other)
- Outcome of the event (resolved, resolved with sequalae, ongoing, death, or unknown)
- Whether or not the event meets serious criteria.

If AE signs and symptoms are the result of a specific diagnosis, the diagnosis only (and not the cluster of signs and symptoms that make up the diagnosis) should be reported on the CRF.
Severity criteria: Severity criteria for adverse events will be defined as follows:

- Mild: awareness of signs/symptoms that are easily tolerated causing minimal discomfort and not interfering with normal daily activities
- Moderate: Sufficient discomfort is present and may interfere with normal daily activities
- Severe: Extreme distress is present causing significant impairment of functioning or incapacitation preventing normal daily activities.

The investigator should use clinical judgement in assessing the intensity of adverse events not directly experienced by the subject (e.g., lab abnormalities).
Relatedness Criteria: An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or definite. Attribution definitions for the relatedness of adverse events will be defined as follows:

- None: An adverse event that is not related to the use of study drug.

- Possible: An adverse event that might be due to the use of the drug; an alternative explanation (e.g. a concomitant drug or illness) is inconclusive. The relationship to time is reasonable.
- Probable: An adverse event that might be due to the use of the drug; an alternative explanation (e.g. a concomitant drug or illness) is less likely. The relationship in time is suggestive.
- Definite: An adverse event that cannot be reasonably explained with an alternate explanation (e.g. a concomitant drug or illness). The relationship in time is very suggestive. A direct cause and effect relationship between the study drug and the adverse event exists.

Serious Adverse Event Reporting: All serious adverse events (SAE) that occur during the trial regardless of their relationship to the study drug must be reported to the IRB (and sponsor) as soon as possible but no later than 24 hours after learning of the event. A Serious Adverse Event (SAE) Report form must be filed and sent to the sponsor as soon as possible. Information included with the initial notification should include as much of the information requested in the form as possible. The SAE Report form should not be held up if all the information regarding the SAE is not yet available. The Investigator will be responsible for reporting to the regulatory authorities, Lupin and all participating investigators all serious adverse events associated with the use of the study drug. The Investigator will report such SAEs using the FDA MedWatch form, CIOMS, etc. The Investigator will report safety reports to the IRB and institution in accordance with IRB regulations and institutional policies.
The Investigator will also record all non-serious adverse events and share with Lupin as a part of the final study report. When additional/new information regarding the SAE becomes available, an updated SAE Report form should be submitted to the sponsor/IRB. Copies of any relevant data from hospital notes (e.g. laboratory tests, discharge summary, ECGs, ER records, etc.) should also be submitted when they become available.
All serious adverse events should be followed and treated appropriately until there is satisfactory resolution of the adverse event, the adverse event becomes stable or can be explained by other causes, clinical judgment indicates further evaluation is not needed, or it appears unlikely that additional information can be obtained given due diligence has been done.
Rates of SAE will be examined after the first 5 subjects are completed, then at 10, 20, and 30 subjects. If greater than 25% of subjects have an occurrence of a SAE at any of these milestones, the study team will work with the IRB to determine whether the trial should stop. If CTCAE grade 3 or higher events occur, we will consult the IRB and FDA and halt the trial if either entity recommends stopping the trial.

10. Data Safety Monitoring

Lupin will perform a monthly reconciliation with the investigator for the SAEs that were shared with Lupin in the given month.
A clinical monitor will perform on-site and/or remote monitoring visits as often as necessary to ensure that all aspects of the protocol are followed. Monitors will record their visits on a site visit log that will be kept on-site, and may be recorded electronically. During monitoring visits, source documentation will be reviewed for verification of data entered on the CRF. Source documents include, but are not limited to, clinic and office charts (paper and/or electronic), laboratory and vaginal culture results, Gram stain results, and any electronic records generated from computerized medical record systems used at investigational sites that may serve as source documentation for the purposes of this protocol.
The review of regulatory documents, informed consents, and drug storage and accountability records will also be done during monitoring visits. Monitors will meet with the principal investigator periodically throughout the study to provide feedback on the study and performance.
Direct access to source documentation and to the drug storage and dispensing area must be allowed during monitoring visits. It is also expected that investigator/study staff will be available to assist the monitor in his/her activities, CRFs will be completed, and ICFs, drug accountability, and regulatory records will be available for review. A suitable area should be provided for the monitor to work during monitoring visits.

11. Study Withdrawal/Discontinuation

All subjects are free to withdraw from participation in the study at any time, and for whatever reason, specified or unspecified, and without prejudice. The reason for discontinuation will be entered onto the study termination page of the CRF.
No constraints will be placed on ordinary subject management, and subjects may be placed on other conventional therapy upon request or whenever clinically necessary, as determined by the investigator/clinician.

12. Statistical Considerations

As this is a pilot project to determine the rates of recurrence with this therapy, no a priori sample size was calculated. We aim to recruit 50 women to determine this rate. That is a similar sample size to other studies in this area. The rates determined by this pilot study will be used in sample size calculations for a larger comparative trial. If the patient population behaves similarly to other BV studies, this study can expect to lose 15% immediately after enrollment as a loss to follow-up. In similar studies, 25.5% had recurrence of BV at the end of the 16-week maintenance phase. A total of 51% had recurrence of BV by the end of the 28-week follow-up phase. In a 50-subject trial, if secnidazole has a similar performance, this would yield approximately 21 subjects that have resolved symptoms through the full 30 weeks of participation.[7] For this pilot study, we anticipate this 50% symptom resolution rate ± 15%. In consideration of this, 21/42 = 0.50 with 95% CI of 0.34 to 0.66 (exact) at 30 weeks, the half-width would be 0.16. We will report rates as point estimates and 95% confidence intervals. For proportions/rates, we will use exact binomial confidence intervals, and, for time to event, we will estimate the confidence intervals using the Kaplan-Meier method.

13. Statistical Data Management

Primary data will be collected via subject self-report and EMR review and stored electronically in REDCap electronic CRF. A backup of the CRF data in REDCap will be saved on a nightly basis to a secure environment maintained by the Research Technologies division of University Information Technology Services (UITS)..

- Quality assurance steps will include:
  - Testing of database prior to being placed into production mode
  - Automated range checks.
  - Manual verification of any self-reported subject data; clinical notes/ electronic medical chart will take precedence over self-reported data, except when overridden by PI or their designee.
  - Single entry with random checks of accuracy and extraction and cleaning of data that will be used for analysis every 6 months.

14. Privacy/Confidentiality Issues

Only study staff involved in the study will have access to study records. Subjects will be given a unique subject number once they sign consent. All study staff will complete and maintain the required Indiana University training and study-specific training prior to interacting with subjects. Study data will be maintained on a secure, password-protected REDCap database.

15. Follow-up and Record Retention

We expect to complete study enrollment in 12 months. Subjects will be followed for up to 9 months. Hard copy records will be kept in secure areas. Electronic records will be kept on password protected systems. Records will be kept until the study ends and follow current guidance. This study utilizes secure IT systems for data gathering, data transfer, data management, and analysis. All data transfers are encrypted. Transfers from data sources are governed by an approved honest data broker process, ensuring data transfers are in accordance with research protocol and relevant data usage agreements. All IT systems used for data gathering, management, and analysis are secure as per HIPAA. Access to patient data and research applications is administered to ensure research teams only have access to patient data for which they are approved.

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