The Use of Coconut Oil for the Prevention and Treatment of Diaper Dermatitis in the NICU Population

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Introduction/Background

Diaper dermatitis is an inflammatory reaction of the skin in the perineal area of infants, and is a common pediatric condition. It can have many causes including infection (yeast, bacterial or viral), friction irritation, skin sensitivity to urine and/or feces, and allergies (perfumes). The overall incidence of diaper dermatitis in infants is estimated to be between 7% and 35%.[1,2] Diaper dermatitis is often a result of increased moisture due to contact with urine and feces, followed by friction. Urine contact with diapered skin raises the skin pH, thus increasing skin permeability and activating fecal enzymes, which are known irritants that can cause skin breakdown.[2] Skin breakdown encourages secondary skin infections that increases the challenge of managing diaper dermatitis. Diaper dermatitis can range in severity from generalized erythema (redness of the skin) to open wounds, and can cause significant pain for babies and distress for parents.

Premature infants have been found to be at higher risk for diaper dermatitis due to their age, and varying degrees of underdeveloped skin structures and functions.[3] In addition, babies that are ill have a higher risk due to increased incidence of diarrhea, cancer, gastrointestinal anomalies, neurological disorders, genetic syndromes and malnutrition.[2] Genesis Neonatal Intensive Care Unit (NICU) infants are often on a number of antibiotics that cause diarrhea, which significantly contributes to the challenges Genesis faces with diaper dermatitis. Genesis estimates its incidence of diaper dermatitis in the NICU is approximately 50%.

The current practice of preventing and treating diaper dermatitis is inconsistent and often not evidence-based. One comprehensive literature review supports treatment of diaper dermatitis through frequent diaper changes, use of super absorbent diapers and protection of the perineal skin with a product containing petrolatum and/or zinc oxide.[2] While numerous studies have established guidelines for neonatal skin care,[2,3,4,5] they often use products that contain numerous chemicals. Due to the increasing problem with bioaccumulation of numerous chemicals in the environment and increased exposure in infants and children, the National Association of Neonatal Nurses has encouraged the removal of chemicals in the NICU. Following this recommendation, Genesis is interested in examining the safety and effectiveness of using unrefined, organic coconut oil for the prevention and treatment of diaper dermatitis among NICU babies at Genesis Medical Center, Davenport.

Coconut oil is the fatty oil obtained from the dried, solid part of the endosperm of Cocos Nucifera. It is a mixture of mainly saturated fatty acids (medium chain triglycerides), with lauric acid being the most abundant. In vitro and in vivo research has provided evidence that lauric acid is effective at killing a wide variety of gram-positive and gram-negative bacteria and *Candida* species.[6] This suggests coconut oil may be an effective anti-fungal to treat diaper dermatitis caused by bacteria. The fatty acids in coconut oil may also act as an effective barrier for skin irritants. Coconut oil has been shown to have a low risk of allergic reaction or adverse effects when applied topically.[6] There have been no published clinical trials on the effectiveness of coconut oil in preventing or treating diaper dermatitis in infants. The majority of research regarding the use of coconut oil in neonates centers around massage.

Studies have shown that coconut oil can be absorbed through the skin of neonates, without any negative side effects.[7,8] One randomized, controlled study found preterm babies massaged with coconut oil daily for 31 days had significantly higher weight gain velocity compared to mineral oil and placebo, and higher length gain velocity compared to placebo.[8] Other studies have found coconut oil to be an effective treatment for atopic dermatitis in pediatric and adult patients. One randomized controlled trial of 117 pediatric patients found topical application of virgin coconut oil for eight weeks was superior to that of mineral oil based on clinical (SCORing of Atopic Dermatitis [SCORAD]) and instrumental (transepidermal water loss [TEWL], skin capacitance) assessments.[9] Another double-blind controlled trial of 52 adults found virgin coconut oil was significantly more effective than virgin olive oil at reducing the prevalence of Staphylococcus aureus (RR=0.10, p=0.0028), indicating coconut oil may have an antimicrobial effect.[10]

Purpose/Objectives

The purpose of the study is to examine the safety and effectiveness of the use of coconut oil for the prevention and treatment of diaper dermatitis among NICU babies at Genesis Medical Center, Davenport.

Primary objectives:

1. To determine and compare the number of days free of diaper dermatitis (“time to rash”) within and between the two treatment groups (i.e., coconut oil and standard of care)
2. To identify the adverse effects of coconut oil when used as a barrier cream for the prevention and treatment of diaper dermatitis

Secondary objectives:

3. To determine and compare the duration of diaper dermatitis within and between the two treatment groups.
4. To determine and compare changes in diaper dermatitis severity within and between the two treatment groups.
5. To determine and compare parent satisfaction scores within and between the two treatment groups at discharge.

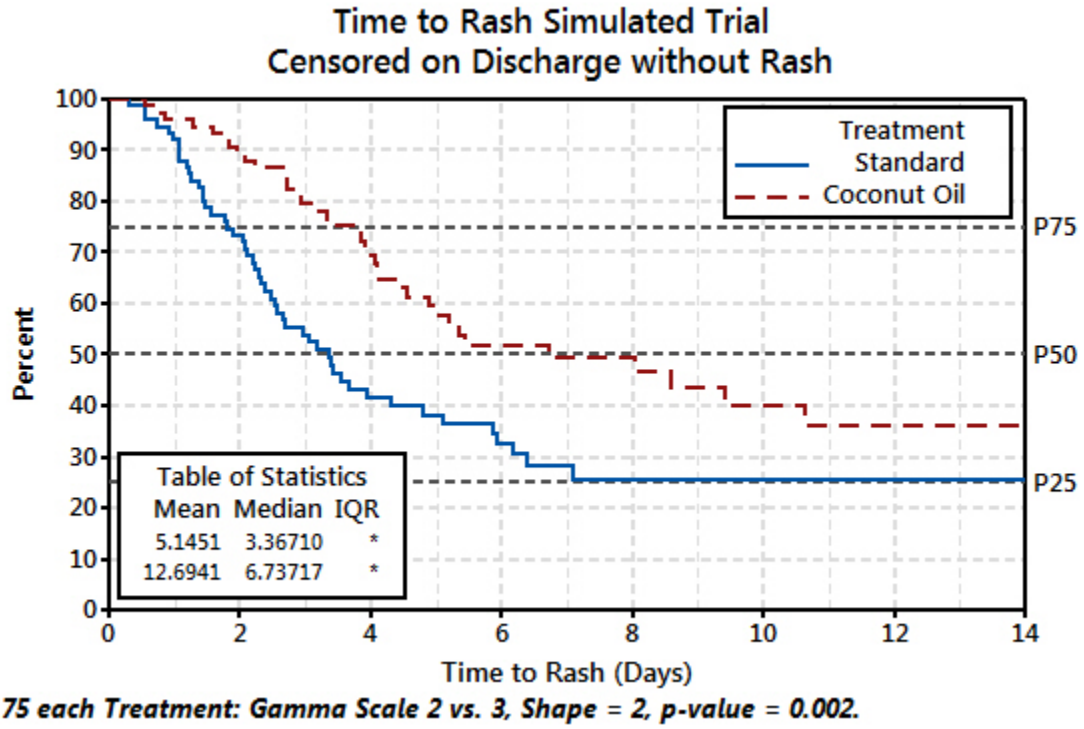
Study Design

This is a prospective, randomized controlled trial to examine the effect of coconut oil on the prevention and treatment of diaper dermatitis in NICU babies at Genesis Medical Center, Davenport. The study will be carried out in the Genesis Medical Center, Davenport NICU. The

Genesis NICU is a Level II Regional Neonatology Center staffed full time by neonatologists from the University of Iowa Children's Hospital. The Genesis NICU provides family-centered treatment for babies born as early as 30 weeks gestation.

Participant Selection and Recruitment

The study will include 150 participants. There are no existing studies examining the time to diaper dermatitis for any treatment options (coconut oil or others), therefore, we conducted the simulation below to estimate a sample size that will have enough power to measure the primary outcomes in the study. The simulation generated time to discharge from a Gamma (3,2) and time to rash for coconut oil of Gamma (2,2) and standard Gamma (3,2). Patients that were discharged before getting diaper dermatitis were censored.



The inclusion/exclusion criteria for the study is outlined below:

1. Inclusion criteria:
    a. Babies admitted to the Genesis NICU
    b. Anticipated stay in the NICU is ≥ 48 hours
    c. Babies wearing diapers 24 hours a day
    d. Parent willing to sign informed consent for the study
    e. Parent willing to use the test products in the diaper area during the trial
    f. Parent willing to not change the type or brand of diaper and wipes during the study
    g. Parent willing to refrain from changing any other products whose use may have an effect of their baby's skin condition during the trial

2. Exclusion criteria:
    a. Babies with a gestational age <30 weeks
    b. Babies with major congenital malformations
    c. Active dermatological conditions other than diaper dermatitis that may affect trial results
    d. Known sensitivity to ingredients in trial products
    e. Babies whose parents have a hazelnut or coconut allergy
    f. Babies whose mother is <18 years of age
    g. Other severe acute medical conditions that may increase the risk associated with trial participation

3. Recruitment

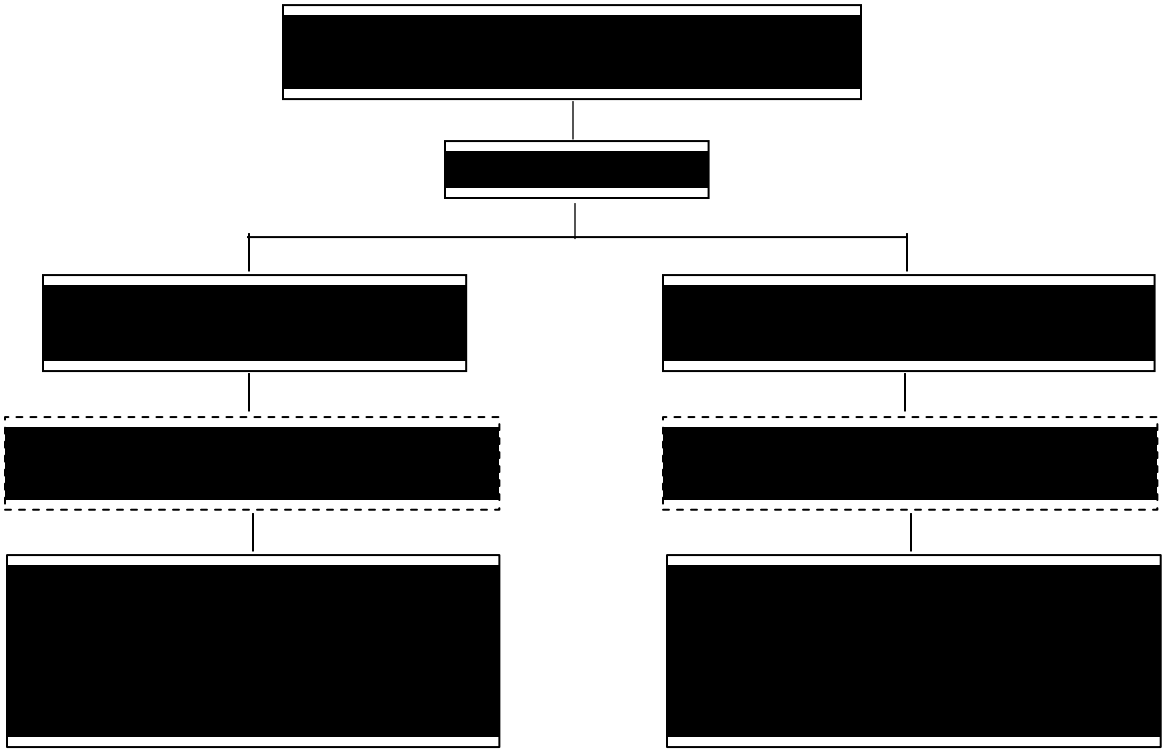
    Participants will be recruited from the Genesis NICU. Each day the nursing staff will identify babies and parents that meet the inclusion/exclusion criteria. The nursing staff will notify the Genesis Clinical Research Coordinators (CRC) of eligible participants. The CRCs will also be screening the NICU patient lists to identify newly admitted babies. The CRC will approach the eligible participants to discuss the study and informed consent. The participants will have up to 24 hours to review the informed consent and decide whether or not to participate.

    Genesis estimates that approximately 200 – 250 babies are admitted to the NICU annually, which suggests that it is feasible to enroll 150 babies in approximately 1.5 years for this study. The estimated accrual rate is 8 babies per month. The research team will be reviewing the accrual rate on a monthly basis. If recruitment is slower than expected, the team will examine the reasons for slow recruitment and make adjustments, as needed. Any changes to recruitment procedures will be presented to the IRB before implementation.

Study Procedure

Participants that are eligible to participate in the study (those meeting the inclusion and exclusion criteria) will review and sign the study consent form. After consenting to participate the participants will be randomized into one of two groups.

The schema below illustrates how participants will be randomized.



Participants meeting the inclusion/exclusion critera that consent to participate in the study will be randomized to one of two Study Arms: Coconut Oil or Standard of Care. The Genesis Business Intelligence Unit will utilize block randomization (blocks of 5) to create 200 cards (50 extra to allow for potential participant attrition) that will include the randomized study arm and a randomly assigned patient number. These cards will be placed in a security envelope and stored in the Research office. Upon receipt of an informed consent, a Clinical Research Coordinator will draw an envelope in sequential order and will notify the participant's parents of his/her study arm. The Clinical Research Coordinator will also place the correct treatment (i.e., coconut oil or standard of care) in the participant's room and will notify the charge nurse in the NICU of the participant's study arm. The Clinical Research Coordinator will use a Randomization Log to record the participant's name, birthdate, study number, study arm and coordinator initials. This log will be kept confidential and secured throughout the study period in the locked Research office.

Participants in each arm will be cleaned with the same Pampers Sensitive brand wipes and will receive the same Pampers brand disposable diaper.The Coconut Oil group will receive coconut oil at each diaper change. An individual sterilized container of unrefined, organic coconut oil will be placed in the participant's room. The coconut oil will be obtained from a large jar and will be placed into the individual sterilized container at the time of randomization. The coconut oil will be labeled with the participant's name and date of birth. At each diaper change participants will

be cleaned with Pampers brand wipes and a generous layer of coconut oil will be applied to the diaper area, including buttocks and creases between thighs and hips. Participants in the Coconut Oil group that develop diaper dermatitis will continue to use coconut oil until they are discharged or reach the primary safety endpoint. They will also be switched from using Pampers Sensitive wipes to a dry washcloth and water, per the standard of care.

The Standard of Care group will receive the current standard of care for diaper dermatitis. The standard of care is no treatment until a diaper dermatitis appears. If diaper dermatitis appears, participants will receive a generous layer of Medline Remedy Phytoplex Z-Guard Skin Protectant, which is an over-the-counter skin protectant with the following active ingredients: white petrolatum 57% and zinc oxide 17%. The participants will also be switched from using Pampers Sensitive wipes to a dry washcloth and water, per the standard of care.

The primary safety endpoint for this study will be skin that is eroded and/or blistered in the diaper area with bleeding. If a participant reaches the primary safety endpoint their study participation will be complete and additional diaper dermatitis treatment options can be used, per currently available treatment options in the Genesis NICU.

The research staff will conduct a quality check each week using a sample of participant rooms to ensure the participants continue to receive care based on the study arm they were assigned to and the diaper dermatitis logs are being completed for every diaper change.

Study Outcomes

Primary Outcomes:

1. The number of days free from diaper dermatitis, as measured by the diaper dermatitis log.
2. The number of participants that develop adverse effects.

Secondary Outcomes:

3. For participants that develop diaper dermatitis, the number of days with diaper dermatitis (duration of diaper dermatitis).
4. For participants that develop diaper dermatitis, the number of days until the participant reaches the primary endpoint (skin eroded and/or blistered with bleeding), as measured by the diaper dermatitis log.
5. The level of parent satisfaction with the diaper dermatitis treatment used, as measured by the parent satisfaction survey.

The study outcomes will be collected for all participants and comparisons will be made between the two study arms.

Data Collection

Every Diaper Change

The nursing staff or Clinical Research Coordinator in the Genesis NICU will collect information about diaper dermatitis at every diaper change using the diaper dermatitis log. The following information will be included in the log:

1. Date
2. Time
3. Presence of pink or red skin[11]
4. Presence of pimply areas on the skin.[11]
5. Presence of eroded and/or blistered skin with bleeding (primary safety endpoint)[11]

Discharge

The Clinical Research Coordinator or nursing staff in the Genesis NICU will distribute the Parent Satisfaction Survey to the parent(s). The Parent Satisfaction Survey will include the following questions:

1. How satisfied were you with your baby's participation in this study?
   5 - Very satisfied
   4 - Satisfied
   3 - Neither satisfied nor dissatisfied
   2 - Dissatisfied
   1 - Very Dissatisfied

2. How satisfied were you with the diaper rash treatment your baby received?
   5 - Very satisfied
   4 - Satisfied
   3 - Neither satisfied nor dissatisfied
   2 - Dissatisfied
   1 - Very Dissatisfied

3. How would you rate the quality of the diaper rash treatment your baby was given?
   5 - Excellent
   4 - Very good
   3 - Good
   2 - Fair
   1 - Poor

4. How effective was the diaper rash treatment at <u>preventing</u> diaper rash for your baby?
   5 - Very effective
   4 - Somewhat effective
   3 - Average
   2 - Somewhat ineffective
   1 - Very ineffective

5. How effective was the diaper rash treatment at treating diaper rash for your baby?
   5 - Very effective
   4 - Somewhat effective
   3 - Average
   2 - Somewhat ineffective
   1 - Very ineffective
   Not applicable – My baby did not get diaper rash
6. How likely are you to use the same diaper rash treatment you received at Genesis at home?
   5 - Very likely
   4 - Somewhat likely
   3 - Undecided
   2 - Somewhat unlikely
   1 - Very unlikely
7. What did you like about your baby's diaper rash treatment?
8. What could we have done better for your baby's diaper rash treatment?

Additional Data Variables

Once the study recruitment goal is met, medical record data will be pulled for each participant. The data collected from the medical record will include all data listed in the table below.

Table One: Data Collection Variables

Variable	**Source**	**Definition**
Patient Name	Cerner Powerchart	Patient's first name, middle initial and last name
Age	Cerner Powerchart	Day of life
Race/Ethnicity	Cerner Powerchart	Documentation of the patients self-identified race and ethnicity
Gender	Cerner Powerchart	Male or Female
Height	Cerner Powerchart	Height in inches at start of study
Weight	Cerner Powerchart	Total body weight (kilograms) at start of study
Length of Stay	Cerner Powerchart	Total days during inpatient hospitalization
Medical History	Cerner Powerchart	Diagnosis, reason for admission, allergies, family history
Major Comorbidities	Cerner Powerchart	Documentation of the patient's major medical conditions
Infection	Cerner Powerchart	Diagnosis of infection - Review temp, WBCs, S/B/Ls, culture and sensitivity results, and physician progress notes; Record as yes or no that infection is or is not present and document infection site
Medications	Cerner Powerchart	List of medications documented in EMR.

Risks

There have been no studies examining the risks of treating diaper dermatitis with coconut oil, and few have evaluated the risks associated with use of Z-Guard. Previous studies using coconut oil topically on neonates for massage found the risk of an adverse event to be rare.[7,8] In addition, there have been studies examining the risks of other treatment options (i.e., Nystatin, Clotrimazole, Miconazole Nitrate) for diaper dermatitis.[12,13] While there is not directly related evidence on the risks of coconut oil or Z-Guard for treating diaper dermatitis, this study will be using the available evidence from the studies referenced above to track the following potential risks: infrequent

Skin around diaper area

- Worsening diaper rash
- Eczema (itchy, red, dry skin)
- Skin inflammation or swelling

Infections

- Yeast (Candida) infection (Dark red patches especially in the folds of skin near the thighs, may include yellow, fluid-filled spots)

General symptoms

- Cough
- Runny nose
- Watery eyes
- Skin redness
- Discomfort

Stomach and Intestines

- Diarrhea

There may be additional risks that we do not know about with the topical use of coconut oil or Z-Guard.

There is also the risk of loss of confidentiality. There is a small chance someone outside of the study team could see the participant's protected health information. Every effort will be made to protect participant privacy and a strict data management plan has been developed and described in the Data Management section of the protocol.

Safety Reporting

The following adverse event definitions will be used for this study:

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs in participants, whether or not related to the use of any study treatments. This includes events related to: • Coconut oil • Usual care (no preventative treatment for diaper rash) • Z-Guard (diaper rash treatment) • The procedures involved (study-required)

Serious Adverse Event (SAE)	Adverse event that:
	• Led to death
	• Led to a serious deterioration in the health of the subject that either resulted in:
	  ○ a life-threatening illness or injury, or
	  ○ a permanent impairment of a body structure or a body function, or
	  ○ in-patient or prolonged hospitalization of an existing hospitalization, or
	  ○ medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
	Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

The following classifications will be used to determine whether the AE was related or unrelated to the use of coconut oil or Z-Guard:

Classification	Description
Unrelated	The adverse event is determined to be due to a concurrent illness or effect of another drug and is not related to study treatments including usual care, coconut oil or Z-Guard.
Related	• The adverse event is determined to be potentially related to the usual care, coconut oil or Z-Guard, and an alternative etiology is equally or less likely compared to the potential relationship to usual care, coconut oil, or Z-Guard, or • There is a strong relationship to usual care, coconut oil, or Z-Guard, or recurs on re-application, and another etiology is unlikely, or • There is no other reasonable medical explanation for the event.

The following definitions will be used to determine the severity of the AE (adapted from the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0):[14]

Term	Definition
Mild	Clinical or diagnostic observations only; no intervention needed
Moderate	Minimal, local or noninvasive intervention needed
Severe	Medically significant but not immediately life-threatening; systemic drug therapy or other treatment needed
Life Threatening	Life threatening consequences; urgent intervention needed
Fatal	Death related to the adverse event

The following definitions will be used to assess whether an adverse event is expected or unexpected:[15]

Classification	Definition
Expected	Any adverse event that is identified in nature, severity or frequency in the study protocol. Any adverse event that is previously known or anticipated to result from the underlying disease, disorder, or condition of the subject(s).
Unexpected	Any adverse event occurring in one or more subjects participating in the study, the nature, severity, or frequency of which is not consistent with either: 1. The known or foreseeable risks associated with the study procedures that are described in the protocol 2. The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

The Clinical Research Coordinator will assess adverse events on a weekly basis for this study by reviewing patient medical records. Serious adverse events will also be identified by nursing staff on the NICU and will be reported to the Clinical Research Coordinator. The Clinical Research Coordinator will report SAEs to Dr. Arikat (Principal Investigator) to determine the need for additional treatment. Adverse events that meet the criteria outlined by the Genesis IRB (i.e., events that are unanticipated, serious or anticipated that occur with greater frequency or severity than expected) will be reported to the Genesis IRB within 10 working days after becoming aware of the information, as per Genesis IRB Standard Operating Procedures.

Data Analysis

Once data is transferred to the GHS Biostatistics Group, research team members will double enter the data and manage the databases, assign identification numbers to participants, perform edit diagnostics and prepare worksheets for analysis.

Comparative analyses of Coconut Oil and Standard of Care groups will include exact tests for comparing binomial characteristics, stochastic ordering for ordinal distributions (exact

permutation tests) and Wilcoxon rank sum tests for continuous factors. All will be analyzed with Cytel Studio StatXact Analyses.

Initially, data will be presented as a Kaplan-Meier plot of time to rash for the log-rank comparison of standard treatment and coconut oil. This will provide the probability of rash by treatment on any given day after the start of the study.

Cox proportional analyses will be used to control for risk factors to determine whether they are effect modifiers or confounders of the treatment effect.

Data Management

Data will be stored in a locked filing cabinet within the Principal Investigator's office in the Genesis NICU and with the Clinical Research Coordinator in the Clinical Research office at Genesis Medical Center East Campus. Once all data is transferred to the GHS Biostatistics Group for data analysis, it will be coded and stored in a secure database. The code linking the participant names and identification numbers will be secured at the GHS Biostatistics Group and only research team members will have access to the code. All research team members have completed NIH Human Subjects Protection training and are committed to protecting the confidentiality of participants and following HIPAA guidelines.

Quality Assurance, Monitoring, & Safety

A Data and Safety Monitoring Board will be convened to oversee this study. The Board will meet at the start of the study and at least bi-annually to review adverse events and the study data. All adverse events will be reported promptly to the Data and Safety Monitoring Board and the Genesis IRB.

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