THE HEALTHY BABY BOTTOMS STUDY:
A TRIAL OF THERAWORX FOAM FORMULATION FOR THE PREVENTION AND TREATMENT OF DIAPER DERMATITIS
(AVADIM HEALTH, INC.)
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1. STUDY OBJECTIVES

1.1 Primary objective: Determine whether parents perceive Theraworx Foam and Spray to be superior to usual care for *prevention* of diaper dermatitis among infants 1-14 months old.

- Hypothesis #1a: Parents will report fewer total days of diaper dermatitis in their infants when the infants are using Theraworx than when they are not.
- Hypothesis #1b: Parents will less likely to report any diaper dermatitis in their infants when the infants are using Theraworx than when they are not.

1.2 Secondary objectives:

Objective #2: Determine whether Theraworx Foam is superior to usual care for *reduction of severity* of diaper dermatitis among infants 1-14 months old.

- Hypothesis #2a: Parents will report less use of adjuvant topical treatments (antifungals, antibacterials, steroids) for their infant's diaper dermatitis when they are using Theraworx than when they are not.
- Hypothesis #2b: Parents will report less severe diaper dermatitis based on visual assessment when their infants are using Theraworx than when they are not.

Objective #3: Determine parents' satisfaction with Theraworx Foam

- Hypothesis #3a: Parents will find Theraworx easy to apply and remove
- Hypothesis #3b: Parents will find Theraworx pleasant to use (smell, feel, appearance)

2. BACKGROUND

Diaper dermatitis is one of the most common dermatologic diseases affecting infants and children (Tuzun et al., 2015). The incidence is highest among those 9-12 months old and it has been reported to affect 7-50% of infants in the US (Tuzun et al, 2015, Cohen, 2017, Blume-Petavi & Kanti, 2018). It is caused by skin exposure to a combination of several factors including: excessive moisture, topical irritants, reduced pH, friction, maceration and bacterial infection (Blume-Petavi & Kanti, 2018). When infants soil their diaper, diaper contents saturate the area raising the pH of the skin above the normal level of 5 or less, and leaving the area highly vulnerable to maceration from friction. Irritants in urine and feces are then able to penetrate the macerated skin, causing inflammation and greater skin friability (Pogacar et al., 2018). An elevation in the skin pH allows pathogenic bacteria to overgrow, and combined with the breakdown in the skin's outer epithelial barrier (statum corenum), can lead to bacterial infection (Pogacar et al., 2018). With the development of more advanced and absorbent diapers in recent years, the incidence of diaper dermatitis has subsequently decreased (Blume-Petavi & Kanti, 2018). Another primary preventive practice for reducing the risk of diaper dermatitis is use of prophylactic barrier creams (Kayaoglu, Kivanc-Altunay & Sarikaya, 2015). Nonetheless, while disposable diaper technology has become more advanced, the composition of barrier creams has not. In fact, some barrier creams such as those containing zinc oxide may actually contribute to the damage cascade leading to diaper dermatitis by increasing the pH of skin (Bartels, et al., 2014).

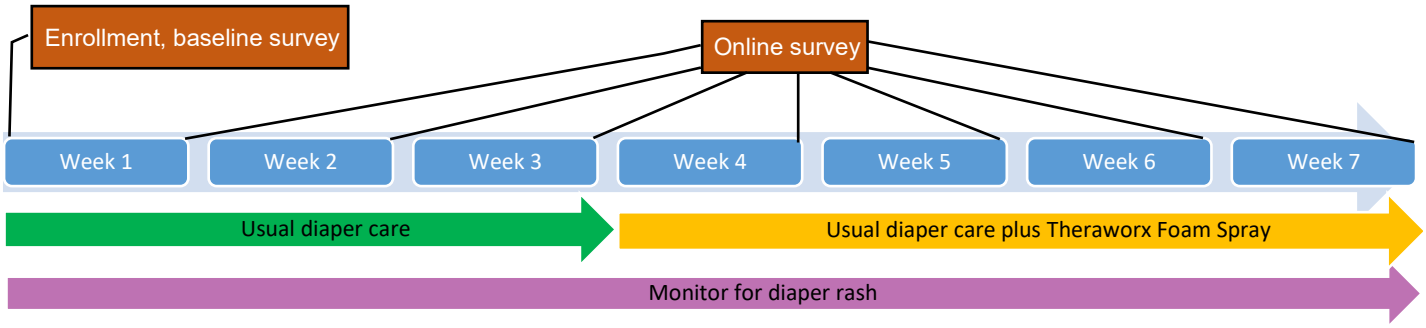
Theraworx Spray Foam by Avadim Health, Inc. is an FDA-registered OTC drug (NDC 61594-000). The marketed product is labelled as a skin protectant with use "for temporary protection of minor cuts, scrapes, burns and chapped or cracked skin" with the active ingredient being allantoin. Allantoin is listed on the FDA OTC Ingredient List as used for or having reviews pending for use as a wound healing agent, skin protectant and external analgesic. As such, Theraworx Foam used in the diaper area may be beneficial for protecting skin against diaper dermatitis wounds, as well as for assisting with wound healing and reducing any associated pain. The purpose of this study is to determine parents' perceptions of the benefits of using Theraworx Spray Foam on their infant's diaper area as part of their hygienic routine, including whether they feel the product is pleasant and easy to use, and whether they feel it helps prevent and reduce the severity of diaper dermatitis in their infants 1-14 months old. This investigation is not intended to be reported to FDA in support of a new indication for use, to support any other significant change in the labeling or to support a significant change in the advertising.

3. PROTCOL DESIGN AND OVERVIEW:

3.1 Study design: This study will be conducted as an open-label, unblinded, sequential trial in which we will employ a pre- vs. post-intervention design involving a run-in period followed by a trial period for all participants. In this way, infants will serve as their own control limiting variability between comparator groups in terms of

diaper hygiene practices including frequency of diaper changes and type of diapers, wipes, and other products used.

3.2 Protocol overview:



3.3 Study Timeline:

Activity	Study month											
	1	2	3	4	5	6	7	8	9	10	11	12
Recruit and enrollment	x	x	x	x	x	x	x	x	x			
Participant run-in period	x	x	x	x	x	x	x	x	x			
Participant experimental period		x	x	x	x	x	x	x	x	x		
Data analysis											x	x

4. PARTICIPANT ELIGIBILITY

4.1 Description of sites enrolling participants: Caregivers of infants ages 1-12 months old will be recruited from one of the five the Children's Health Centers (CHCs) at Children's National Health System. These health centers together treat ~30% of all children ages 0-18 years old in DC with Medicaid insurance. The population is predominantly minority (African American (85%), Hispanic (8%)) and publically insured (83%).

4.2 Inclusion criteria: Caregivers will be eligible if they can read English at the 8th grade level, and have reliable access to the internet and email for 7 weeks. English proficiency and internet access will be verified by parental completion of the first online survey within 24 hours of the request. Caregivers must also be a custodial guardian of an infant between the ages of 1-12 months old who lives with them, currently wears diapers, and has had ≥1 diaper rash in the 2 months preceding recruitment.

4.3 Exclusion criteria: Caregivers will be excluded if their infant is immunocompromised, has a congenital disorder, or, on the day of recruitment, has a diaper rash, has a moderate to severe illness requiring hospitalization or transfer to the emergency room, or was circumcised <10 days prior. Participants who do not complete the first online survey or ≥2 post-intervention online surveys will be excluded from participating in the remainder of the study. They will also be excluded if they do not have a stable address at which they can receive a package of Theraworx at week 4 and/or are unable to pick it up at Children's National.

5. PROCEDURES

5.1 Recruitment and enrollment: Potential participants will be initially identified when bringing their children to one of the five Children's Health Centers for care. On days of recruitment (which will be determined via a convenience sample based on study personnel scheduling), study personnel will access electronic health records to identify potential participants based on the age of their child. Parents of children ages 1-12 months old will be approached for study participation in a private treatment room or in the waiting room. Potential participants will be told briefly that they may qualify to participate in a 7 week study to help determine the effectiveness of a new diaper rash product called Theraworx that is currently being used as a skin protectant and for wound care. They will be told that the study will involve using Theraworx with every diaper change for 4 weeks, and also answering 8 surveys starting with a baseline, in-person survey on the day of enrollment, followed by 7 weekly, online surveys. Those who are interested in learning more about the study will be invited to a private space (if not already in one) to conduct the screening process, and if applicable, the informed consent process (Appendix A). Study eligibility will be assessed using an online screening form with stop logic

(Appendix B). For those who meet eligibility requirements, study staff will obtain written informed consent, verbally administer the baseline, in-person survey, obtain several forms of contact information, demonstrate how the Theraworx Foam should be used, and train participants in rating rash severity using a modified Diaper Dermatitis Scale (Buckley 2016) (Appendix C).

5.2 Run-in and trial periods: There will be a 3 week run-in period starting just after enrollment during which time parents will be instructed to continue their usual diapering care including use of any other diaper products/creams, and to respond to the weekly survey requests. After completing the run-in period, parents will choose to either pick up from the hospital or be sent via Fed-Ex a sufficient supply of Theraworx to last the 4 week duration of the trial period. Parents will receive written instruction on how to apply the Theraworx with every diaper change (Appendix D) and to continue to respond to the weekly survey requests.

5.3 Surveys

5.3.1 Baseline, in-person survey: Immediately following the informed consent process, study staff will verbally administer the baseline, in-person survey to participants (Appendix E). This survey will assess infant race/gender, diet (breast/bottle feeding/solid food), daily stool frequency, history of parental and sibling atopic dermatitis/childhood eczema, frequency of diaper dermatitis, creams/products used in diaper area (bath soap, emollients, diaper wipes); and who is involved in changing diapers (parent, grandparent, sibling, babysitter, daycare, etc.). It will also determine participant preference to pick up the Theraworx or have it sent to their home, and assess participant accuracy with rating visual severity of diaper rashes according to the modified Diaper Dermatitis Scale after being trained by staff. Lastly, participants will be asked to recall total number of days their infant had a diaper rash over the last 7 days, and if the number is greater than 0, to rate the rash using the modified Diaper Dermatitis Scale.

Upon completion of the baseline, in-person survey, the participant will receive an incentive debit card (ClinCard) which will be activated for the patient and charged with $10. The participant will be instructed to keep this card for the next 7 weeks to receive future incentive disbursements for completing the online surveys.

5.3.2 Weekly, online surveys: Starting on the first Monday morning that falls at least 8 days from completion of the baseline, in-person survey and repeating each of the following Monday mornings for a total of 7 occurrences, a unique online survey link will be emailed to each participant. Each Sunday beforehand, participants will be texted and emailed a reminder to check their emails the next day and to complete the survey within 24 hours of receiving the emailed link. Each Monday morning, participants will receive a second text message reminder. By each Tuesday at noon, a list will be generated of survey non-respondents who will be contacted by phone twice that day by study staff to complete that week's survey on the phone. Each Wednesday morning, ClinCards will be charged with incentive awards for participants who complete the entire online survey. Participants who do not complete at least the first online survey will not be eligible to complete any further surveys and will be dropped from the study. This will help limit participation to those who can demonstrate capacity and willingness to complete the online survey with the intent of minimizing loss-to-follow up over the 7-week period of individual enrollment.

Weekly online surveys will assess whether the infant had any diaper dermatitis over the past 7 days, and if so, the total number of days with rash, and severity of rash on its worst day (using a modified Diaper Dermatitis Scale score (0-8)). It will also assess for any: use of other products and adjuvant therapies in the diaper area, diarrheal illnesses, new foods initiated, and changes to their contact information. The surveys during the run-in period (weeks 1-3) will confirm whether the participant prefers to pick up the Theraworx or have it sent to their home (Appendix F). During the trial period (weeks 4-6), the weekly survey will also assess how frequently Theraworx was used, and whether it was applied as a foam and/or spray (Appendix G). The final survey at the end of week 7 will be slightly longer since it will also assess satisfaction with Theraworx (in terms of its smell, feel, appearance, ease of use, whether they would recommend it to a friend, and how it compares to other diaper creams they have used) (Appendix F).

5.4 Participant reimbursement: To promote completion of online surveys and reduce risk of participant loss-to-follow up, an escalating incentive scale will be used. Completion of the baseline, in-person survey and the

first 3 weekly online surveys will be compensated with a $10-per-survey incentive. Completion of the next 3 surveys will be compensated $15 each. Completion of the longer, final survey will be compensated with a $30 incentive. Thus, the maximum reimbursement for any one participant over the entire duration of participation will be $115. All incentives will be disbursed on ClinCard debit cards.

Survey name	Baseline	Week 1 online	Week 2 online	Week 3 online	Week 4 online	Week 5 online	Week 6 online	Final
survey format	in person	online	online	online	online	online	online	online
reimbursement	$10	$10	$10	$10	$15	$15	$15	$30

5.5 Participant schedule of activities:

Procedures	T0: Screening/ Enrollment/ Baseline: Day 1	T1-1	T1: Day 8*	T2-1	T2: Day 15*	T3-1	T3: Day 22*	T4 -1	T4: Day 29*	T5-1	T5: Day 36	T6-1	T6: Day 43*	T7-1	T7: Final Study Contact: Day 50*
Informed consent	x														
Baseline survey	x														
Survey reminder text/email/call		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Weekly survey (including AE self-report)			x		x		x		x		x		x		x
Start intervention							x								

***** Actual day may be up to 8 days later to allow T1 to occur on the first Monday at least 8 days from T0.

6. PHARMACEUTICAL INFORMATION

Commercially available Theraworx foam spray will be provided to participating sites by Avadim Technologies Inc.

6.1 Administration: Theraworx will be dispensed for use during the intervention period as several smaller volume bottles such that the product can be kept in several settings including the home and daycare if needed. The formulation will be dispensed in bottles with and without the foam actuator so parents can choose to apply it as a spray or foam per their own preference. During the trial period, parents will be reminded to apply Theraworx with every diaper change alone, or as a base layer if they choose to apply it with other products or creams.

6.2 Potential/Reported Toxicities

- Acute Eye: Direct eye contact may cause minor irritation. If eye contact occurs, rinse thoroughly
- Acute Skin: No reports of adverse reactions to skin contact.
- Acute Inhalation: None Known
- Acute Ingestion: None Known
- Chronic Effects: None known
- Medical Conditions Aggravated by Effects: None Known

6.2.5: Product Ingredient List

- Aqua (Water)
- Cocamidopropyl Betaine
- Aloe Barbadensis Leaf Juice
- Colloidal Silver
- Tocopheryl Acetate
- Glycerin

- Allantoin
- Beta-Glucan
- Citrus Paradisi (Grapefruit) Fruit Extract
- Lauryl Glucoside
- Tetrasodium EDTA
- PEG/PPG-4/12 Dimethicone
- Methylparaben
- Propylparaben
- Parfum (Fragrance)

6.3 Agent accountability: The PI will ensure that Children's National will maintain a careful record of the inventory and disposition of Therworx using a Drug Accountability Record Form. The Children's National Clinical Research Unit Pharmacy will use this form to track lot numbers, expiration dates, and overall inventory during the study, at the end of the study and prior to destruction.

6.4 Treatment Compliance: Parents will administer Theraworx spray foam to their children. They will report use on the weekly surveys.

7. ADVERSE DRUG REACTION REPORTING

7.1 Defining and reporting of unexpected and serious adverse events

Unexpected Adverse Events (UAEs) are defined as events that are not listed in the consent form, and are possibly related to the intervention, or are listed but occur more frequently or are more severe than anticipated. Serious Adverse Events (SAEs) are defined to include death, life threatening illness, hospitalization or prolongation of hospitalization, and persistent/significant disability. Because all intervention will occur at the participant's home unsupervised by study staff, UAEs and SAEs will be reported by the parent on the weekly online surveys. Any self-reported SAEs will be documented by study staff using the Children's National Serious Event Reporting System (SERS). Investigators will follow the Children's National guidelines for reporting SAEs. The guidelines are to report the death of a Children's National subject enrolled in an interventional study if the death is **unexpected** (not due to disease progression) and **related or possibly related to the research** within one (1) business day of learning of the event. A follow-up report must be submitted within two (2) business days. All other UAEs and SAEs will be be reported to the IRB within seven (7) business days of learning of the event. The investigator will notify the study sponsor at the same time as appropriate. Risks that are described in the protocol and consent form (expected AEs), as well as SAEs and UAEs that are unrelated to the intervention do not need to be reported to the IRB, unless the expected AE occurs more frequently or is more serious than expected. However, we will report all AEs to the DSMB, and subsequently to the IRB in the annual continuing review. Any proposed changes in the consent form or research procedures as a result of AEs will be prepared by the study team and submitted to the IRB for approval.

7.2 Stopping Criteria

7.2.1 Individual Stopping Criteria

- All protocol interventions are complete
- Failure to complete the first online survey or ≥2 post-intervention online surveys
- Death
- Lost to follow-up
- Study withdrawal
- Serious Adverse Event
- Discretion of the Study PI, such as the PI decides that continuing in the study would be harmful or no longer in the participant's best interest

7.2.2 Study stopping criteria:

- The data show a significantly increased risk of serious adverse effects during the experimental phase of the study.
- It becomes clear that successful completion of the study is not feasible (e.g. there is an excess of patient dropout, missing data, lack of recruitment, etc).

8. PATIENT CONFIDENTIALITY

To maintain patient privacy, we will be use the database product REDCap as the platform for data entry, validation and storage. The REDCap server of Children's National is located in a locked room in the Clinical Research Institute and is password protected. Access to the server is controlled by the group membership system residing on the server. In order to gain access to the data on this server, a valid user must be added. REDCap security systems require setting up a user account and password for each user to log onto the server and then he/she will be given specific permission to access the databases. This permission can only be given to data staff by the server administrator with the permission of the PI. While analyses are being conducted, data will be stored on password protected computers and backed up on the Children's National secure server which, like the REDCap server, is controlled by a group membership system requiring setting up a user account for access. Once analyses have been completed, the data will be removed from the hard drive(s) of any computer(s) used for analysis, and will be stored as de-identified electronic files on the CNHS secure server. The investigator will grant monitors and auditors from Avadim Technologies Inc. access to participant records as needed to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

9. STATISTICAL ANALYSIS PLAN

9.1 Outcome assessment: Outcome of interest will be diaper dermatitis as assessed by parental visual assessment using a modified Diaper Dermatitis Scale Score (see Appendix C).

9.2 Sample size and power calculation: PASS 15 was used to estimate sample size needed to detect a difference of two days of perceived diaper rash between pre- and post-test scenarios using paired t-tests with non-parametric adjustment. Allowing for a large standard deviation of up to 5 days and a moderate degree of correlation between measures, a sample size of 65 with measures at both time-points would allow for detection of statistical difference at 80% power with a two-tailed p-value of 0.05. Assuming a 35% loss to follow up over the 7 weeks participation duration, we plan to recruit 100 participants. If recruitment loss exceeds 35% at the interim, we will consider raising this number to 150 participants.

9.3 Statistical Considerations

Hypothesis 1a: Parents will report fewer total days of diaper dermatitis in their infants when the infants are using Theraworx than when they are not. To evaluate Hypothesis 1a, total reported dermatitis days over the 4 week pre- and post-intervention time-points will be separately summed. For the primary analysis, only participants who completed all 8 weekly surveys will be included. Secondary analyses may consider all participants with at least two reports in each of the study periods, with missing values assumed to be the mean number of dermatitis days reported by the participant by study period. Number of dermatitis days during usual care (pre-intervention) will be compared to number of dermatitis days following use of the Theraworx Spray Foam (post-intervention) using either paired t-test or Wilcoxon signed rank test, as appropriate.

Hypothesis 1b: Parents will be less likely to report any diaper dermatitis in their infants when the infants are using Theraworx than when they are not. Occurrence of any dermatitis during the two study periods will be coded as "yes" (at least one dermatitis day) or "no" (zero dermatitis days) based on parent report of number of dermatitis days. Differences in occurrence pre- and post-intervention will be explored using McNemar's test. If numbers permit, conditional logistic regression will be considered to evaluate odds of dermatitis when using Theraworx Spray Foam compared to usual care.

Hypothesis 2a: Parents will report less use of adjuvant topical treatments (antifungals, antibacterials, steroids) for their infant's diaper dermatitis when they are using Theraworx than when they are not. Use of adjuvant topical treatments during each of the study periods will be considered as both a binary variable (any or none) as well as frequency of use, defined as number of weeks in which use was reported. Any use

pre- vs. post-intervention will be evaluated using McNermar's test or conditional logistic regression. Number of uses will be compared using Wilcoxon signed rank test. Depending on numbers, marginal homogeneity tests may also be considered, treating the number of weeks as categorical variables. As use during unreported weeks will be unknown and difficult to quantify, primary analyses will consider only participants who completed all surveys.

Hypothesis 2b: Parents will report less severe diaper dermatitis based on visual assessment when their infants are using Theraworx than when they are not. Dermatitis severity will be considered in two ways: 1) average severity during each study period and 2) maximum severity during each study period. Both average and maximum severity based on the total score from the visual assessment scale will be compared pre- and post-intervention using Wilcoxon signed rank test. As in 1a, for the primary analysis, only participants who completed all 8 weekly surveys will be included. Secondary analyses may consider participants with at least two reports in each of the study periods to allow for severity averages during each study period to be calculated.

Hypothesis 3a: Parents will find Theraworx easy to apply and remove
Hypothesis 3b: Parents will find Theraworx pleasant to use (smell, feel, appearance) Descriptive statistics (median Likert scale scores and proportions) based on parent report will be used to summarize participant satisfaction with Theraworx Spray Foam.

For all analyses, a two-tailed p-value of < 0.05 will be considered significant. Sensitivity analyses based on reported Theraworx Spray Foam use, infant age, and infant sex will be considered. Difference in number of reported diaper rash days between usual care and Theraworx will be compared between high and low Theraworx use groups using Wilcoxon-Mann-Whitney test to assess whether high Theraworx usage improves number of diaper rash days better than low usage More complex longitudinal models considering weekly outcomes during usual care versus Theraworx Spray Foam using Generalized Estimating Equations may also be considered.

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