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An intervention to reduce phthalate and bisphenol exposure during the critical period of minipuberty

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), any other applicable US government research regulations, and institutional research policies and procedures. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
EDC	Endocrine-Disrupting Chemical
EMR	Medical Record Number
FFR	Federal Financial Report
FWA	Federal wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
LOD	Limit of Detection
ISM	Independent Safety Monitor
MOP	Manual of Procedures
MRN	Medical Record Number
N	Number (typically refers to participants)
NIH	National Institutes of Health
NYU CHES	New York University Children's Health and Environment Study
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research

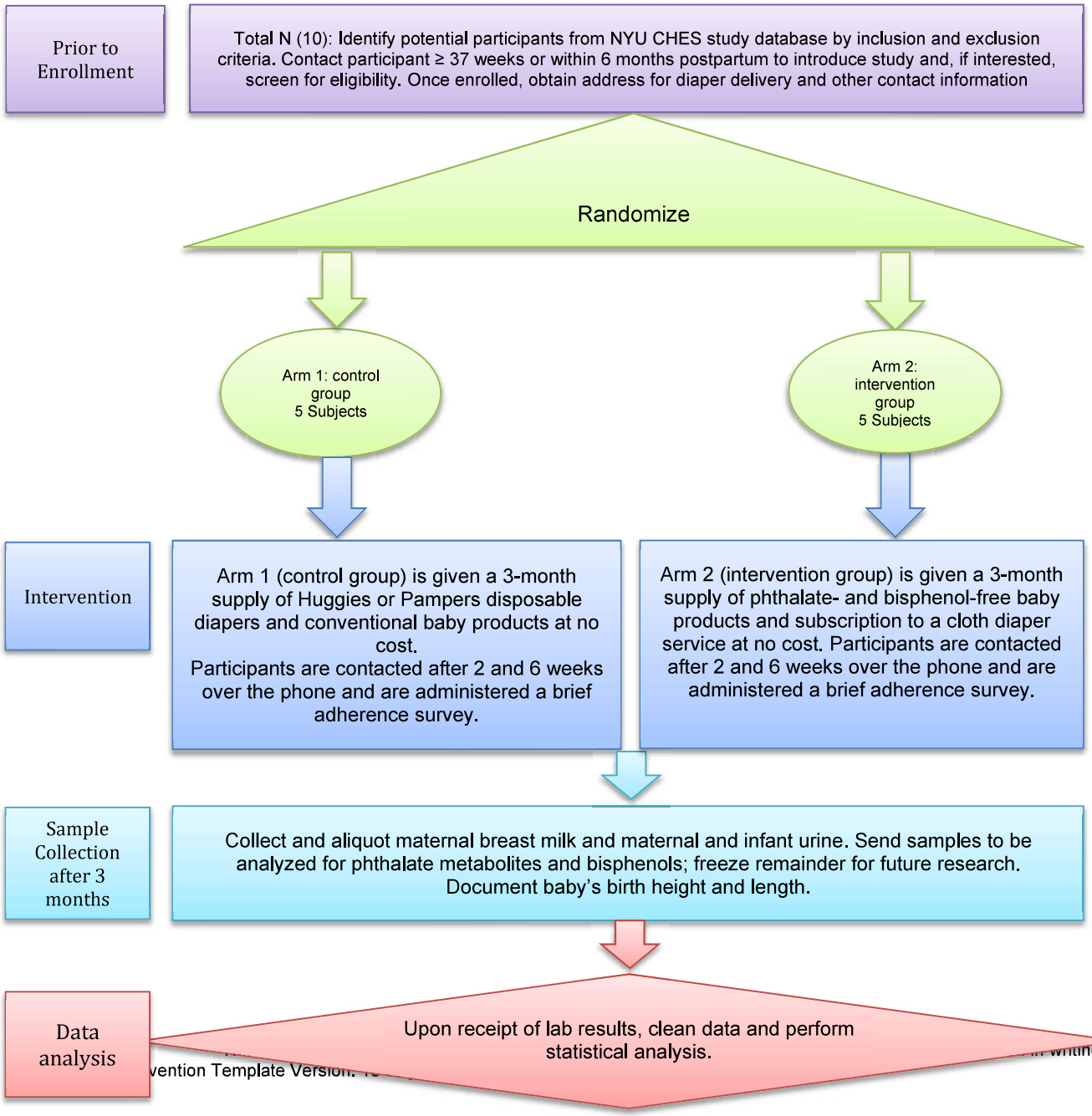
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States

Protocol Summary

Title	An intervention to reduce phthalate and bisphenol exposure during the critical period of minipuberty
Short Title	Diaper Study
Brief Summary	Phthalates and bisphenols have been detected in a range of infant care products. This pilot study will test whether intervening on these sources of exposure during the critical period of minipuberty affects infants' body burden of phthalates and bisphenols. We will recruit 10 participants from the ongoing NYU Children's Health and Development Study (CHES) cohort study who are >=37 weeks gestation or <6 months postpartum, carrying a singleton fetus or with a singleton infant, and intending to breastfeed or breastfeeding. We will randomly assign them to use either conventional baby products or phthalate- and bisphenol-free baby products for the first or next three months of their children's lives. Toward the end of the intervention, we will collect maternal breast milk and infant urine, and assay samples for phthalate metabolite and bisphenol concentrations.
Phase	N/A
Objectives	Aim 1: To assess the feasibility of an intervention designed to reduce infant phthalate and bisphenol exposure Aim 2 (exploratory): To compare urinary phthalate and bisphenol exposure levels in the intervention and non-intervention groups, as well as between mothers and children in the control group.
Methodology	Open-label randomized controlled trial

Endpoint	Participants are enrolled until they have been using the assigned diapers for 3 months, toward the end of which time we will collect maternal breast milk and maternal and infant urine to test for phthalate metabolite and bisphenol concentrations
Study Duration	1 year (allows for 6 months of data collection among 10 participants and 6 months of data analysis).
Participant Duration	3 months
Population	We will recruit 10 participants who are already enrolled in the NYU CHES study at the Brooklyn campus. Eligible participants will be >=37 weeks gestation or <6 months postpartum, carrying a singleton fetus or with a singleton infant, and intending to breastfeed or breastfeeding.
Study Site	NYULH-Brooklyn
Number of participants	10 participants
Description of Study Intervention/Procedure	Half of the participants will be randomly assigned to the intervention group and will receive a three-month supply of phthalate- and bisphenol-free baby products (e.g., wipes, diaper cream) and a subscription to a cloth diaper service.
Reference Therapy	Half of the participants will be randomly assigned to the control group and provided with a three-month supply of conventional disposable diapers (e.g., Huggies or Pampers) and baby products (e.g., wipes, diaper cream).
Key Procedures	Three-month adherence to diaper assignment and one-time infant urine collection and maternal breast milk collection.
Statistical Analysis	Our primary aim is to assess the feasibility of the intervention; the project is not adequately powered to detect statistically significant differences between groups. However, we will compare distributions of chemicals between the two infant groups to assess the effectiveness of the intervention and also between mothers and children from the control group to assess the relative prevalence of particular bisphenols or phthalates in diet (reflected in maternal breast milk concentrations) vs. baby products (reflected in infant urinary concentrations).

Schematic of Study Design



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1 Introduction, Background Information and Scientific Rationale

1.1 Background Information and Relevant Literature

In keeping with David Barker's fetal programming hypothesis,[1] studies of associations of phthalates and bisphenols with child health outcomes have focused on *in utero* exposure. Results have been inconclusive, however,[2,3] with inconsistencies commonly attributed to varying approaches to exposure assessment and other methodological issues. An alternative explanation that has not been explored is the possibility that pregnancy may not be the only—or even the primary—critical period for early-life endocrine disruption. Minipuberty, a brief window during the first six months of life when sex hormones surge in sync with gonadal cell proliferation, may be a particularly vulnerable period for dysregulation of the hypothalamic-pituitary-gonadal axis by endocrine-disrupting chemicals (EDCs).[4] Because of their estrogenic and anti-androgenic properties, bisphenols and phthalates have the potential to adversely affect the development of reproductive tissue responsible for sex hormone production, with downstream consequences for child health in multiple domains.

While most conceptual models linking EDCs to reproductive health outcomes have focused on prenatal exposure, including Niels Skakkebaek's Testicular Dysgenesis Syndrome theory[5] and Germaine Buck-Louis's companion Ovarian Dysgenesis Syndrome theory,[6] gestation is not the only critical period in the development of reproductive endocrine glands. Testicular Leydig and ovarian granulosa cells undergo three phases of maturation, culminating in sexual maturity. The first is mid-pregnancy, when Leydig cells proliferate in the fetal testis[7] and primordial follicles emerge in the fetal ovary.[8] The second is during minipuberty, when Leydig cells undergo another burst of proliferation and differentiation, and granulosa cells also proliferate as part of the postnatal surge in folliculogenesis.[9] Finally, both become fully activated in puberty. During minipuberty, reproductive hormone concentrations rise precipitously, peaking between two and three months postnatally,[4] only to become quiescent after about six months of age until reactivated during puberty. Disruption of this intricate choreography by exposure to EDCs could have negative consequences for the development of a variety of tissues and organs that are regulated by sex hormones, including brain, bone, adipocytes, and gonads.

Little research has been done on potential causes and effects of endocrine disruption during minipuberty. The only study to date to examine associations between EDCs and sex hormones during minipuberty reported positive associations between urinary bisphenol A (BPA) and both estradiol and the estradiol:testosterone ratio in the first three months of life.[10] These results are consistent with BPA's estrogenic profile; the study did not measure phthalates, which are more commonly anti-androgenic. Sex hormones in minipuberty, in turn, have been linked with child health outcomes. Nearly all of the research in this area has focused on neurodevelopment, demonstrating links between lower testosterone levels in male infants and compromised auditory processing and language development.[11-15] Sex hormones also affect metabolism. One small study that examined minipuberty sex hormone levels and adipose tissue development found that testosterone and luteinizing hormone were negatively associated with body mass index, and estradiol was positively associated with skinfold thicknesses in boys.[16]

This pilot intervention study will assess the magnitude of infants' exposure to bisphenols and phthalates through common infant care products. If research continues to show child health consequences of bisphenol and phthalate exposure during minipuberty, these products could eventually be targeted for regulation.

1.2 Rationale

Infants are highly exposed to phthalates and bisphenols, ubiquitous EDCs that have both estrogenic and anti-androgenic activity. Phthalates and bisphenols have been detected in a range of infant care products, including diapers,[17,18] wipes, baby lotions, soaps, shampoos,[19] and plastic baby bottles.[20] Exposure is magnified by infants' high surface-to-volume ratio and by the increased efficiency of dermal absorption via the thin skin surrounding their enlarged genitalia.[21] This pilot study will test whether intervening on these sources of exposure during the critical period of minipuberty affects infants' body burden of phthalates and bisphenols. If successful, this protocol may be scaled up and eventually evidence may be used to inform regulation of chemicals contained in infant care products and educational outreach programs to protect children's health.

Aim 1: To assess the feasibility of an intervention designed to reduce infant phthalate and bisphenol exposure.
H1: We will successfully recruit participants from within an existing cohort study and collect biosamples from participants and their children in a single follow-up study visit.

Aim 2 (exploratory): To compare urinary phthalate metabolites and bisphenols between the intervention and non-intervention groups, as well as between mothers and children in the control group.
H2: Chemical levels will be higher among infants in the control group vs. the intervention group. There will be no difference in average chemical concentrations between the two groups of mothers. Among controls, different chemicals will be present in breast milk vs. infant urine.

1.3 Potential Risks & Benefits

1.3.1 Known Potential Risks

There is no excess risk to participants in this study due to the intervention being tested, which is designed to reduce the risk of endocrine disruption. The phthalate- and bisphenol-containing disposable diapers and baby products that the control group will receive are by far the standard in the US. We hypothesize that the phthalate- and bisphenol-free diapers and baby products that the intervention group will receive will reduce their risk of health outcomes associated with EDC exposure.

There is a risk of loss of confidentiality or privacy in relation to personal information and specimens to be collected upon participation in this study. We will make every effort to protect participants' privacy by labeling their samples and information only with a code, and keeping the key to the code in a password-protected database accessible only to IRB-approved study personnel.

There is no excess risk to participants associated with completing questionnaires. Participants may feel frustrated from answering questions. If that happens, participants are free to skip any questions they do not wish to answer.

1.3.2 Known Potential Benefits

Participants may gain the knowledge that they will be contributing to research that may improve our understanding of the relation between baby products, EDC exposure, and minipuberty.

2 Objectives and Purpose

2.1 Primary Objective

The primary objective of this study is to assess the feasibility of an intervention designed to reduce infant phthalate and bisphenol exposure during the potential critical period of minipuberty. Specifically, we aim to evaluate the feasibility of an intervention that targets EDC exposure through randomly assigning participants to receive conventional diapers and baby products or cloth diapers and phthalate- and bisphenol-free baby products from birth through age 3 months.

2.2 Secondary Objectives

The secondary and exploratory objective for this study is to compare urinary phthalate and bisphenol exposure levels in the intervention and non-intervention groups, as well as between mothers and children in the control group

3 Study Design and Endpoints

3.1 Description of Study Design

- This is a single-site pilot intervention study to be conducted at NYU Langone Health-Brooklyn.
- Participants will be recruited from the ongoing pregnancy/birth cohort study, NYU CHES study.
- Participants will be randomly assigned to an intervention group (N=5) or a control group (N=5).
- Participants will receive a 3-month supply of either disposable diapers and conventional baby products (control group) or cloth diapers and phthalate- and bisphenol-free baby products (intervention group) at no cost.
- Participants will complete brief adherence surveys at three postnatal time points.
- After 3 months, study personnel will conduct a study visit during which maternal breast milk and maternal and infant urine will be collected.
- Urine and breast milk samples will be analyzed for phthalate metabolites and bisphenols in the NYU Human and Environmental Exposure Assessment Facility Core lab.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

The primary endpoint, needed to fulfill Aim 1, is when the total number of participants (N=10) have used their assigned baby products for three months and the two biospecimens (maternal breast milk and infant urine) have been collected from all participants.

3.2.2 Secondary Study Endpoints

The secondary endpoint, needed to fulfill Aim 2, is when the biospecimens have been analyzed for phthalate metabolites and bisphenols.

3.2.3 Exploratory Endpoints

N/A

4 Study Enrollment and Withdrawal

4.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Enrolled in NYU CHES study at the NYULH-Brooklyn campus
2. Over 18 years of age
3. At least 37 weeks gestation or <6 months postpartum
4. Carrying singleton fetus or having given birth to a singleton infant
5. Intending to breastfeed or breastfeeding
6. English or Spanish speaking
7. Intending to obtain/obtaining pediatric care for infant at the Sunset Park Family Health Center at NYU Langone

4.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Not enrolled in NYU CHES study from the NYULH-Brooklyn campus
2. Under 37 weeks gestation or having had a preterm birth
3. Carrying multiples or having given birth to multiples
4. Not intending to breastfeed or not currently breastfeeding
5. Not comfortable communicating in English or Spanish
6. Not intending to obtain/obtaining pediatric care for infant at NYULH Sunset Park Family Health Center
7. Under 18 years of age

4.3 Vulnerable Subjects

This study includes pregnant women and neonates, who are vulnerable subjects. We do not anticipate that this study will pose greater than minimal risk to the mother, fetus, and later neonate, as both disposable and cloth diapers are commonly used among our study population. Additionally, collection of neonatal urine and maternal breast milk involves no more than minimal risk. Urine will be collected via a bag that gently adheres to the skin around the infant's penis; breast milk will expressed manually by the participant. Participation in this study is entirely voluntary. Participants will be able to withdraw from the study at any time without negative consequences. Our study design is in compliance with all items included in 45 CRF part 46.204 (research involving pregnant women or fetuses) and 46.205 (research involving neonates.) Any risk to neonates is

expressly in pursuit of benefits that would directly benefit them; i.e. regulation of chemicals in baby products. Furthermore, while this research does not hold out the prospect of benefit for the pregnant woman or the fetus, risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means. A pregnant person's consent will be obtained in accord with the informed consent provisions of subpart A. The risk in this study is the least possible for achieving the objectives of the research. No inducements, monetary or otherwise, will be offered to terminate a pregnancy. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy. Individuals engaged in the research will have no part in determining the viability of a neonate.

4.4 Strategies for Recruitment and Retention

Potentially eligible participants will be identified by Diaper Study personnel from among those already enrolled in NYU CHES study at the Brooklyn campus. All Diaper Study personnel will be added to the NYU CHES study. Potential participants will be recruited either by phone or at an in-person prenatal visit at ≥37 weeks gestation or within 6 months postpartum.

- **Remote Screening**
    - Potential participants will be contacted via phone using an IRB-approved telephone recruitment script. If they are interested in hearing more about the study, study staff will ask screening questions over the phone to confirm eligibility.
    - If potential participants are eligible and still interested in learning more about the study, potential participants will be sent the REDCap link to the Key Information Sheet and Informed Consent and will be given the phone number of a study team member to call after they have reviewed the consent materials. Refer to Section 12.3.2 for more information on the consent procedures.
    - If potential participants are not eligible and/or do not wish to take part in the study, their PHI (phone number, address, and any other PHI) will be discarded at this point.
- **In-Person Screening**
    - If possible or preferred by the potential participant, screening may occur in person at the NYULH Brooklyn location. This will be coordinated by study staff.
    - Study staff will give the potential participant a physical copy of the Key Information Sheet and Study Infographic if it has not already been sent to them. If the potential participant is interested, study staff will ask screening questions to confirm eligibility.
    - If the potential participant is eligible and still interested in learning more about the study, the study staff member will walk the potential participant through Informed Consent. If the potential participant wishes to take part in this study, she will be asked to sign a paper copy of the Informed Consent. Refer to Section 12.3.2 for more information on the consent procedures.

In order to retain enrolled participants, we will visit them in the hospital following delivery or via phone call if a birth visit is not possible in order to inform participants of their group assignment and contact them again two weeks and six weeks after birth to check in on the diaper delivery logistics and assess and encourage group assignment adherence.

4.4.1 Use of DataCore/Epic Information for Recruitment Purposes

This study will not use NYULH's DataCore/Epic information for recruitment purposes. We will use participant information from our ongoing study NYU CHES study for recruitment purposes.

4.5 Duration of Study Participation

The estimated time of enrollment is 1-3 weeks prior to delivery or within 6 months postpartum. Participants and their infants will be enrolled for three months.

4.6 Total Number of Participants and Sites

10 mother-infant pairs will be enrolled in this study. It is expected that all participants will provide usable data.

4.7 Participant Withdrawal or Termination

4.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from the study at any time upon request and with no consequence.

An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

4.7.2 Handling of Participant Withdrawals or Termination

If a participant withdraws between the time of consent and biospecimen collection, the participant will be replaced.

4.7.3 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the PI. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- PI decision
- Insufficient compliance to protocol requirements

Study may resume once concerns about data quality are addressed and satisfy the sponsor and/or IRB.

5 Behavioral/Social Intervention

5.1 Study Intervention Description

The study intervention is supply of baby products. The intervention group (n=5) in this study will be assigned use of phthalate- and bisphenol-free baby products and subscription to a cloth diaper service. Participants assigned to the control group (n=5) will receive disposable diaper delivery and conventional baby products.

5.1.1 Administration of Intervention

This intervention (supply of baby products) will be delivered via mail and/or delivery service. The frequency of delivery will depend on the delivery service. The delivery will cover three months' worth of diapers and baby products.

6 Study Procedures and Schedule

6.1 Study Procedures/Evaluations

6.1.1 Study Specific Procedures

Biospecimen Collection:

- Biospecimens (1.8mL of maternal breast milk, 1.8mL of maternal urine, and 1.8 mL of infant urine) will be collected at one study visit approximately 2-3 months after enrollment. Biospecimen collection will occur either after a routine well-visit or at the participant's home. If a home visit occurs, study staff will go to the participant's home. Refer to Section 6.2 for more details.

Data Collection:

- Participant's electronic medical record will be used to monitor when they have delivered.
- Either the infant's medical record or the NYU CHES study records will be used to obtain birth weight and length for analysis.
- NYC CHES study questionnaire data that participants previously completed under the NYU CHES study will be pulled from the NYU CHES study database.

- We will create a new database for the Diaper Study where we will store all Diaper Study-related results along with demographic and NYU CHES study questionnaire data to be pulled from the NYU CHES database.

Questionnaire Administration:

- Participants will be asked to complete a brief adherence questionnaire at three postpartum time points.
  - Questionnaire will be administered over the phone by study personnel 2 weeks and 6 weeks after diaper intervention has begun.
  - Questionnaire will also be administered during the single study visit.
- It will take less than 5 minutes to complete questionnaire.
- Questionnaire responses will be entered into REDCap by study personnel.
- The purpose of the questionnaire is to assess if the diaper delivery service is working smoothly for the mother and to gauge adherence to group assignment.
- Questionnaire data collected from this study will be shared with qualified researchers on the NYU CHES study.

6.1.2 Standard of Care Study Procedures

No clinical procedures are carried out in this study.

6.2 Study Specific Biospecimens

6.2.1 Specimen Collection Procedures

Participants will be asked to manually express breast milk into a polypropylene specimen cup (Starplex Scientific Corp., Cleveland, TN).

Maternal urine will be collected via standard procedure in a sterile cup.

To collect infant urine, a Pediatric Urine Collector (Precision Dynamics Corp., Valencia, CA) will be provided to participants. This device is composed of a clear plastic bag with a foam-lined opening that adheres to the skin around the infant's genital area without puckering, providing a leak-proof seal.

Diaper Study personnel will not be involved in the maternal specimen collection procedures. Diaper Study personnel will facilitate the collection of infant urine.

6.2.2 Specimen Preparation, Handling, and Storage

Urine and breast milk will be aliquoted into bisphenol- and phthalate-free 2 mL tubes (Thermo Scientific, Waltham, MA) within two hours of collection and will be stored at -80^{o}C. Urine and breast milk collection containers/devices will be tested for the presence of phthalates and bisphenols.

6.2.3 Specimen Shipment

N/A

6.2.4 Laboratory Evaluations

Chemical analyses. Phthalate metabolites and bisphenols will be analyzed at the NYU Human and Environmental Exposure Assessment Facility Core lab under the supervision of Sunmi Lee.

Bisphenols. Eight bisphenols (BPA, BPAF, BPAP, BPB, BPF, BPP, BPS, and BPZ) will be determined by HPLC-ESI-MS/MS. Concentrations of individual bisphenols will be adjusted for creatinine (Cr) as described below. We will also sum molar concentrations of all individual bisphenols for a total bisphenol concentration.

Phthalate metabolites. Quantitative detection of 22 phthalate metabolites will also involve HPLC-ESI-MS/MS.[22] Urine samples will be processed using enzymatic deconjugation of glucuronidated phthalate monoesters, followed by solid phase extraction coupled with reverse-phase HPLC-ESI-MS/MS. Individual phthalate metabolite concentrations will be adjusted for Cr as described below. We will also sum metabolites of parent compounds di-2-ethylhexyl phthalate (DEHP), as well as di-isononyl phthalate (DiNP) and di-*n*-octyl phthalate (DNOP), as DiNP, DNOP, and di-isodecyl phthalate (DiDP, represented by its metabolite mono-carboxyl isononyl phthalate [mCINP]) are increasingly replacing DEHP in response to consumer advocacy and legislative activity.[23]

Creatinine. To account for urinary dilution, urinary Cr will be analyzed using HPLC-ESI-MS/MS as described elsewhere[24] and chemical concentrations will be adjusted for Cr via a transformation described by Kuiper et al.,[25] with an alternate adjustment method by O'Brien et al.[26] and no adjustment explored in sensitivity analyses.

6.3 Study Schedule

6.3.1 Screening

- Diaper Study personnel will identify potential participants from the NYU CHES study database.
- Remote or in-person screening will take place. Refer to Section 4.4 for details.

6.3.2 Enrollment/Baseline

- Diaper Study team member will obtain consent.
- Diaper Study team member will assign participant to study group in alternating fashion. Participants will not be told of their group assignment in advance of delivery or postpartum consent.
- Diaper Study team member will obtain participant's delivery date from participant's EMR and schedule diaper delivery to their home to begin directly afterward or schedule diaper delivery to begin immediately if consent occurs postpartum.

6.3.3 Phone Call - 2 Weeks After Delivery

- Diaper Study team member will confirm consent.
- Participants will complete questionnaire by phone.

6.3.4 Phone Call - 6 Weeks After Delivery

- Diaper Study team member will confirm consent.
- Participants will complete questionnaire by phone.

6.3.5 Study Visit

- After using products in assigned study group for up to three months, a single study visit will occur after a routine well-visit or at participant's home between 2 and 3 months after diaper intervention has begun. If visit cannot occur after infant's well-visit, Diaper Study team member will go to participant's home.
- Diaper Study team member will confirm consent.
- Participants will be asked to provide maternal breast milk and urine samples.
- Diaper Study team member will collect infant urine sample.
- Participants will complete questionnaire.

6.3.6 Withdrawal Visit

- No procedures or evaluations will be done and no biospecimens will be collected if a participant withdraws or is terminated early.

6.3.7 Unscheduled Visit

- We do not anticipate unscheduled visits.

7 Safety and Adverse Events

7.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event

- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

7.1.1 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

7.1.2 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

7.2 Classification of an Adverse Event

7.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.

- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

7.2.2 Relationship to Study Intervention

The clinician's assessment of an AE's relationship to study intervention is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study intervention assessed. In a clinical trial, the study intervention must always be suspect. To help assess, the following guidelines are used.

- ***Related*** *– The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.*

- ***Not Related*** *– There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.*

7.2.3 Expectedness

Expected adverse reactions are AEs that are common and known to occur for the study intervention being studied and should be collected in a standard, systematic format using a grading scale based on functional assessment or magnitude of reaction. Describe the method of determining the expectedness of an AE. Expectedness refers to the awareness of AEs previously observed, not on the basis of what might be anticipated from the properties of the study intervention.

7.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

7.4 Reporting Procedures – Notifying the IRB

7.4.1 Adverse Event Reporting

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to study participation should be recorded and reported immediately.

7.4.2 Serious Adverse Event Reporting

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

7.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;

- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within<insert timeline in accordance with policy> of the IR's receipt of the report of the problem from the investigator.

7.4.4 Reporting of Pregnancy

N/A

7.5 Reporting Procedures – Notifying the Study Sponsor

N.A

7.6 Reporting Procedures – Participating Investigators

N/A

8 Study Oversight

There will be no formal data and safety monitoring board for this protocol, as there is only minimal risk associated with participation in the current study. We will employ an internal Data Safety Monitoring Plan, managed by Dr. Linda Kahn, and communicate with staff to ensure adequate risk assessment, adverse event reporting, compliance with protocol, and drop-out rates, with monthly review of safety data and appropriate reporting requirements to the NYU Langone Health IRB. Should unanticipated reportable events, defined as internal or external events (such as deaths, life-threatening experiences, injuries, breaches of confidentiality, or other problems), occur at any time during or after the research study, Dr. Kahn will report them immediately to the NYU Grossman School of Medicine IRB. Any new information indicating a change to the risks or potential benefits of the research, any deviation from the protocol, and any possible serious or continued non-compliance will be reported to the NYU Langone Health IRB by Dr. Kahn immediately.

9 Statistical Considerations

9.1 Statistical and Analytical Plans

There will not be a formal SAP in this study, as it is a pilot with only 10 participants. Demographics will be compared between members of the intervention and control groups to assess the success of the randomization process. T-tests will be used to compare phthalate metabolite and bisphenol levels between the two groups and correlations of chemical levels will be run comparing mothers and infants in the control group.

9.2 Statistical Hypotheses

Aim 1: H1: We will successfully recruit participants from within an existing cohort study and collect biosamples from participants and their children in a single follow-up study visit.

Aim 2: Chemical levels will be higher among infants in the control group vs. the intervention group. There will be no difference in average chemical concentrations between the two groups of mothers. Among controls, different chemicals will be present in breast milk vs. infant urine.

9.3 Analysis Datasets

We will perform both ITT analysis as well as Per-Protocol Analysis, based on participants' self-reported compliance, which will be assessed periodically throughout the intervention.

9.4 Description of Statistical Methods

9.4.1 Analysis of the Primary Efficacy Endpoint

Our primary aim is to assess the feasibility of the intervention. There are no relevant statistical endpoints.

9.4.2 Analysis of the Secondary Endpoints

Our secondary endpoints are concentrations of bisphenols and phthalate metabolites in breastmilk and infant urine. We will perform t-tests to compare distributions of chemicals between the two infant groups to assess the effectiveness of the intervention. We will also assess correlations of concentrations of individual bisphenols and phthalate metabolites between mothers and children from the control group to assess the relative prevalence of these chemicals in diet (measured in maternal breast milk) vs. baby products (infant urine).

9.4.3 Safety Analyses

There is no risk associated with the intervention being implemented in this study, so there will be no safety analysis.

9.4.4 Adherence and Retention Analyses

We will calculate the percent of participants that complete the study as well as the average adherence to protocol in each of the two arms based on participant self-report.

9.4.5 Baseline Descriptive Statistics

T-tests and chi-square tests (as appropriate) will be used to assess differences in demographic characteristics between participants in the intervention and control groups.

Because this is a pilot analysis, it is not adequately powered to detect statistically significant associations or to permit controlling for covariates or multiple comparisons. The sample size (10 total; 5 per group) has been determined based on budgetary considerations.

9.4.6 Enrollment/Randomization/Masking Procedures

Participants will be assigned to either the intervention or control group on an alternating basis upon enrollment. Because of the nature of the intervention (cloth vs. conventional diapers), they will not be blinded. If a participant needs to be replaced, the replacement will be assigned to the same group as the participant who withdrew.

9.4.7 Evaluation of Success of Blinding

N/A

9.4.8 Breaking the Study Blind/Participant Code

N/A

10 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participants who consent to this study are already enrolled in NYU CHES Study, and are also consenting to allowing their data to be shared between the Diaper Study and NYU CHES Study. Examples of data that can be shared between the two studies include biospecimen and questionnaire responses.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Quality Assurance and Quality Control

Bisphenols. Eight bisphenols (BPA, BPAF, BPAP, BPB, BPF, BPP, BPS, and BPZ) will be determined by HPLC-ESI-MS/MS. In our experience with Sunmi Lee's laboratory, coefficients of variation are minimal/good for bisphenols (1–15%). With the use of isotopically labeled internal standards, limits of detection (LODs) measured in a recent NYU CHES sample ranged from 0.04-0.50 ng/mL, sufficient for measuring urinary bisphenols in non-occupationally exposed subjects.[27] Calibration checks as well as method control and fortified samples ensure results are within ±15% of the nominal value, with duplicates performed within each batch to ensure precision within ±15%.

Phthalate metabolites. Quantitative detection of 22 phthalate metabolites will also involve HPLC-ESI-MS/MS.[22] Urine samples will be processed using enzymatic deconjugation of glucuronidated phthalate monoesters, followed by solid phase extraction coupled with reverse-phase HPLC-ESI-MS/MS. Coefficients of variation from samples analyzed in Sunmi Lee's laboratory are minimal/good for phthalates (1–15%); LODs measured in a recent NYU CHES sample ranged from 0.02–0.74 ng/mL. Calibration checks as well as method control and fortified samples ensure results are within ±15% of the nominal value, with duplicates performed within each batch to ensure precision within ±15%.

12 Ethics/Protection of Human Subjects

12.1 Ethical Standard

The PI will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46.

12.2 Institutional Review Board

The protocol, key information sheet(s), informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. IRB approval will be obtained before any participant is enrolled in this study. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent materials will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

12.3 Informed Consent Process

12.3.1 Consent and Other Informational Documents Provided to Participants

Consent materials describing in detail the study purpose, study procedures, and potential risks are given to the participant and written documentation of informed consent is required prior to starting the study protocol. The following consent materials are submitted with this protocol:

- Key information sheet (English)
- Consent document for mother and infant (English)
- Participation timeline infographic (English)
- Contact card for participants to reach out to study staff

We will submit translated documents for IRB review and approval via a Modification at a later time.

12.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive description of risks and possible benefits of participation will be provided to the participants. Consent materials will be IRB-approved and potential participants will be asked to read and review the consent documents, which will be either emailed to them or handed to them physically, as described in section 4.4.

An IRB-approved Diaper Study team member will begin the informed consent process with a concise and focused presentation of the key information using an IRB-approved *Key Information Sheet*. If potential participant is interested in learning more about this study, she will have her eligibility assessed by study staff. If potential participant is eligible and interested, the study team member will fully explain the research study using the IRB-approved *Informed Consent* template as the consent script and answer any questions that may arise.

All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form, ask questions, and discuss the study with their family members, friends, or doctor prior to signing or providing verbal consent. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

If potential participant is eligible and would like to take part in this study, and the informed consent process takes place in person:

- Individual will be asked to sign a paper copy of the Informed Consent.

If potential participant is eligible and would like to take part in this study, the informed consent process takes place remotely (by phone), and the individual has the ability to provide an electronic signature:

- Individual will be asked to sign the electronic consent (eConsent) via REDCap. The REDCap eConsent link will be submitted to the IRB for review in Research Navigator via Modification before use in the study. Language consistency with the IRB-approved consent will be reviewed and approved by the IRB before use.

If potential participant is eligible and would like to take part in this study, the informed consent process takes place remotely (by phone), but the individual does not have the technical ability to provide an electronic signature:

- Individual will verbally indicate their interest in participating in the study to the staff member who is conducting the informed consent. The staff member will record this in the participant record on REDCap. The participant will sign the printed consent form at the earliest opportunity (e.g., her next prenatal visit, in the hospital following delivery, etc.) before any biospecimens are collected.

At the time of consent, participant will also provide consent for her future child's participation. A copy of the signed informed consent document will be given to the participants for their records either at the time of consent if screening and consent takes place in person or at the earliest possible in-person encounter, which is when those providing verbal consent will sign a physical copy of the form and those who eConsented will receive a printout of their signed eConsent form. A copy of the signed informed consent document will be stored in the participant's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g., use of a translator, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

12.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality will be strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, or representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored in the Division of Environmental Pediatrics at NYULH for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

All raw data gathered for the study will be kept in a locked cabinet in the Division of Environmental Pediatrics. All computerized data files will be maintained on a password-protected computer system on both NYULH MCIT-managed network shared drive set up for this study and on REDCap and will only be accessible to trained study personnel. All participants will be assigned a unique identifier (code number) that will be used in all computerized files containing study data. A file containing links between participant identity and code number will be maintained in a separate file with a separate password and will only be accessible to trained study personnel who must know the participants' identities to contact participants for enrollment, to schedule appointments, to conduct follow-up calls, and/or to manage the data. All study personnel will receive training in human subjects' protection prior to any involvement with participants or study data and will be continuously supervised by Dr. Kahn.

This study will not affect treatment or determine prognosis for an individual participant. Data and samples collected in the study are being used for research purposes only. The results from this study will not be shared with participants' medical providers. Participants will not receive the results of their chemical analysis.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

12.4.1 Research Use of Stored Human Specimens or Data

- Samples and data collected under this study may be used to study EDC exposure in minipuberty.
- Access to stored samples and data will be limited to the PI and sub-investigators
- Samples and data will be stored using codes assigned by the investigators. All computerized data files will be maintained on a password-protected computer system on both NYULH MCIT-managed network shared drive set up for this study and on REDCap and will only be accessible to trained study personnel.

12.5 Future Use of Stored Specimens or Data

- Sample storage is optional and subjects may request their samples be removed from storage at any time by contacting the study team.
- Data and specimens collected in the Diaper Study will become part of a broader biobank housed in the Division of Environmental Pediatrics, owned by the NYU CHES PI, Dr. Trasande. This research biobank is being created so that researchers in the Division of

Environmental Pediatrics can study the life course from preconception, pregnancy, childhood, and adult

- If an NYU investigator requires de-identified Human Biospecimens from the NYU Langone Environmental Pediatrics Biobank, they will place a request to the NYU CHES PI, Dr. Trasande. All requests should include an overview of the proposed research including study aims, background, methods, type and amount of samples requested, statistical considerations justifying the number of samples requested, and contact information of all involved investigators, study personnel, and source of funding.

- Researchers from outside institutions carrying out specific research that is not contrary to NYU Langone policies and scientists from industry will also be considered. Transfers of Human Biospecimens to outside institutions require a duly authorized agreement between NYU/NYU Langone and the recipient of the Human Biospecimens.

- Requests for use of data or stored biospecimens for scientific purposes will be considered by a committee chaired by Dr. Kahn, the PI of this study, that includes faculty with relevant experience

13 Data Handling and Record Keeping

13.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the study personnel at the site under the supervision of the PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Clinical data and clinical laboratory data will be entered into REDCap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source

13.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close out or 5 years after final reporting/publication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.3 Protocol Deviations

A protocol deviation is any noncompliance with the study protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site personnel. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

All deviations must be addressed in study source documents and reported to the NYULH IRB. Protocol deviations must be reported to the local IRB per their guidelines. The PI and study personnel are responsible for knowing and adhering to their IRB requirements.

13.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

14 Study Finances

14.1 Funding Source

This study is internally funded through an NYU CEHRT pilot grant.

Contact: Anna Carrasco (anna.carrasco@nyulangone.org)
227 East 30th Street
209-914-2415

14.2 Costs to the Participant

We do not anticipate any costs to the participant in this study.

14.3 Participant Reimbursements or Payments

Participants in this study will receive no reimbursements or payments.

15 Study Administration

15.1 Study Leadership

This pilot study is led by Dr. Linda Kahn, who is fully responsible for its administration. Sunmi Lee will be Dr. Kahn's Sub-Investigator, providing expertise in quantifying phthalate metabolites and bisphenols in human biosamples. This study will also be supervised by Sub-I Dr. Leo Trasande, the PI of NYU CHES.

16 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULH investigators will follow the applicable conflict of interest policies.

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18 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents may not require protocol amendments.

- Adherence survey
- Recruitment script

- Key information sheet
- Informed consent
- Study Infographic
- Contact card for participants