Prevention of Prematurity and Xylitol (PPaX) Trial

ClinicalTrials.gov ID NCT02333227

Last Update or Approval: 11/1/2021

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

Protocol Number: H-35933
Status: Approved
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Approval Period: 11/1/2021 - 10/31/2026

Section Aa: Title & PI

A1. Main Title

PREVENTION OF PREMATURITY AND XYLITOL (PPAX) TRIAL

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A3a. Financial Conflict of Interest

Does any member of study personnel (Investigator (including investigator's spouse and/or dependent children)) that are involved in the design, conduct, or reporting of the research have a Significant Financial Interest (SFI) that would reasonably appear to be affected by the research for which funding is sought and/or associated with an entity/business that would reasonably appear to be affected by the research?

No

Section Ab: General Information

A4. Co-Investigators

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A5. Funding Source:

Organization: THRASHER RESEARCH FUND

A6a. Institution(s) where work will be performed:

BCM: Baylor College of Medicine
Baylor College of Medicine Children's Clinical Centers of Excellence Network

A6b. Research conducted outside of the United States:

Country: MALAWI
Facility/Institution: Baylor International Pediatrics AIDS Initiative (BIPAI) Malawi Center of Excellence
Contact/Investigator: Peter Kazembe
Phone Number:

If documentation of assurances has not been sent to the Office of Research, please explain:
The process for IRB approval from Malawi has been granted and received and the approval has been attached in Section S.

The qualifications of all the staff are included in the protocol itself and in the attached summary. The staff conducting research in Malawi is Dr. Peter Kazembe, BCM. In addition, the other people assisting will be the other faculty listed on the protocol. All other physicians, connections, and support staff within each country are described in the protocol and summary; many are Baylor College of Medicine faculty, and largely will not be conducting research as much as they will be assisting with country logistics.

Although there is therapeutic intent, all subjects enrolled are in Malawi and thus Medicaid/Medicare does not apply.

A7. Research Category:

A8. Therapeutic Intent

Does this trial have therapeutic intent?
No

A9. ClinicalTrials.gov Registration

Does this protocol/trial require registration on ClinicalTrials.gov due to it: meeting the definition of an Applicable Clinical Trial, being required under the terms and conditions of an award, or being proposed to be published in ICMJE journals?
No, this clinical is not a clinical trial, or does not meet the definition of an Applicable Clinical Trial, or does not need to be registered under the terms and conditions of an award, or is not a clinical trial with results intended to be reported in an journal belonging to the ICMJE. Registration is not required.

Section B: Exempt Request

B. Exempt From IRB Review

Not Applicable

Section C: Background Information

The burden of perinatal morbidity and mortality related to preterm birth is astounding. In 2005, the WHO estimated that 9.6% or 12.9 million births worldwide were born preterm at <37 weeks of gestation, and were accompanied by as a high as a 42% mortality rate (http://www.who.int/bulletin/volumes/88/1/08-062554). Despite regional advances and slight decreases in the U.S. preterm birth rate in the last two years, adverse birth outcomes related to the length of gestation (preterm birth and near-term birth) are recognized as one of the most significant disorders in maternal-child health at global scale. Worldwide, more than 20 million infants are born each year with low birth weight, with more than 95% of these being delivered in developing nations (1, 2). Of the 4 million newborn deaths annually, nearly 1/3 (27%) are directly attributable to prematurity with another 36% secondary to opportunistic infections (sepsis, pneumonia, gastrointestinal) related to prematurity and low birth weight (1). 75% of the 4 million deaths occur within the first week of life, with the vast majority occurring in the first 48 hours (1, 2). In poor rural communities, infant mortality related to preterm and low birth rate birth exceeds that in urban communities, and is not solely attributed to limited access to secondary and tertiary care (1). Because the empiric recurrence risk of preterm birth approximates 40-50% (3), global primary prevention of preterm birth is essential (4).

Identifiable causes of preterm birth are generally ascribed to one of three categories: 45-50% idiopathic, 30% in association with preterm premature rupture of the membranes, and 15-20% are iatrogenic or maternally indicated (5). However, multiple factors including modifiable behaviors (smoking), maternal periodontal disease, prior history of preterm birth, multiple gestations, race/ethnicity (African-American women have a higher risk than Caucasians), and foreshortened cervical length (where at <25 weeks 2.0 cm is the 5th%, and 2.5 cm is the 10th%) have been postulated to influence the occurrence of preterm births (6-9). The combination of two or more factors can possibly synergistically or additively increase the risk for spontaneous preterm birth. For example, in addition to identifying polymorphisms rendering susceptibility of risk for the delivery of preterm and growth restricted births (10,11), we have previously demonstrated that maternal tobacco use in pregnancy meaningfully alters the placental epigenome and subsequent gene expression (12,13). Accurate determination of the relative and additive or synergistic

contribution of underlying etiologies, such as periodontal disease and oral health with behavioral and socioeconomic factors are hampered by a fundamental lack of understanding of the process of parturition (5, 12-16). As such, the cause(s) of as great as 80% of spontaneous preterm births remain classified as ¿unknown¿ (1-5). However, maternal oral health is emerging as a leading contributor to risk of spontaneous and infectious-related preterm birth on a global scale (7-9; 17-26).

Pertaining to the soundness of the observations, 195 studies in the 16 years since Offenbacher¿s original observations (17) have been published (PubMed search, March, 2014) and the overwhelming majority demonstrate a link between poor maternal oral health and risk of preterm birth (example references 17-33).

As noted, a relationship between maternal oral health and risk of preterm birth and low birth weight infants has long-been demonstrated (17, 18; 27-29) in both industrialized nations (17-19) and rural and developing regions (27-30). In initial data from two single-center clinical trials, periodontal treatment in gravidae with dental caries reduced the rate of preterm birth (31,32). However, more definitive analysis from three large, multicenter randomized controlled trials have failed to show a benefit to non-surgical treatment for periodontitis (inflammation secondary to periodontal infection), specifically ¿scaling and root planing¿ (i.e., removal of dental plaque and calculus from the tooth enamel and root; 19, 20, 33). In sum, three observations persist: ¿ Peridontal disease in gravidae poses risk of preterm birth and delivery of a low birth weight infant globally; ¿ However, treating periodontal disease by scaling and root planing in gravidae who manifest such oral microbial inflammation poses no benefit to the prevention of preterm birth, but also no harm (i.e., it improved periodontal disease but did not decrease nor increase the risk of preterm delivery); ¿ It is unknown whether primary prevention of dental caries and periodontitis may show benefit (identified gap in our knowledge and justification for our proposed study).

Periodontitis (defined as a destructive inflammation of the peridontium) has a prevalence of 30% or greater in women of child bearing age (8, 34). By definition, it involves microbial infiltration of the peridontium, which stimulates a chronic inflammatory response, recurrent bacteremia, and the production of cytokines and prostaglandins which trigger risk of preterm birth (17-34). It is the same production of prostaglandins (primarily PGE2 and reactive intermediates) which are felt to mediate the risk of preterm birth (2-9).

In the last year, we and others have made breakthroughs towards understanding the link between maternal oral health and risk of preterm birth (35-45). A recent cross-sectional study of 195 patients (35) demonstrated Gram-positive and Gram-negative intracellular bacteria harbored in the basal plate (which comprises the tissue layer directly at and below the maternal-fetal interface). These were observed in nearly 1/3 of placental specimens, with a high prevalence among preterm deliveries <28 weeks gestation but regardless of clinical or pathologic evidence of chorioamnionitis (35). Although current paradigms suggest that the majority of intrauterine infections which are associated with preterm birth originate in the lower genital tract and ascend into an otherwise ¿sterile¿ intrauterine environment (36), we have most recently demonstrated that the majority of taxa detected in the placenta with DNA-based technology are not found in the urogenital tract, but rather represent commensal species common to the oral cavity (37-42). Some of these oral microbes, such as Fusobacterium nucleatum (a Gram-negative oral anaerobe) may facilitate hematogenous transmission during placentation as a result of their ability to bind vascular endothelium and alter permeability, thereby functioning as an ¿enabler¿ for other common commensals, such as Escherichia coli (37; 42-45). The results of our study (37) indicate that the placenta harbors a low-abundance but metabolically rich microbiome. The placental microbiome is largely comprised of non-pathogenic commensal microbiota from the Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes, and Fusobacteria phyla. In aggregate, the placental microbiome profiles were most akin (Bray-Curtis (B-C) dissimilarity <0.3) to the non-pregnant human oral microbiome. 16S-based OTU analyses revealed a strong and significant correlation of the placental microbiome with with risk of preterm birth <37 weeks (p=0.001;These latter findings further highlight the likely underlying biologic and molecular mechanisms linking maternal oral health to preterm birth which serves as additional rationale to our clinical trial as proposed herein.

So if we know that there is biologic evidence linking maternal oral health to preterm birth, but treating active periodontal disease does not reduce these morbidities, is it possible that primarily preventing periodontitis (or lessening its severity) might prevent preterm birth? If so, what are the least expensive, practical, and efficacious preventative measures? Globally, many strategies related to prevention of dental caries have focused on reduction of dietary simple sugars. One class of substitutes is the polyols (i.e., sugar alcohols), the most common and efficacious of which include xylitols used in chewing gum such as Spry and ¿sugar free¿ gummy snacks. What makes the polyols attractive candidates for the prevention of oral disease (notably in a rural population) is based on these well-grounded observations (references 46-52): ¿ In rural communities, where running water, lack of toothpaste and toothbrushes, and inadequate dental care are realities of everyday life, distribution of polyol gum or gummy candies is an attractive alternative; Although research gaps exist on optimal dosing, meta-analyses and multiple prospective and randomized controlled trials demonstrate that xylitol containing chewing gum prevent periodontitis (level I evidence); ¿ While the mechanism of action by which the polyols reduce dental caries is uncertain, it is clear that they are efficacious. Hypothesized mechanisms include increasing salivary flow by masticiation, enhancing alkaline pH to minimize demineralization/promote remineralization of tooth enamel, and altering the oral microbiome via diminishing abundance of virulent species Streptococcus mutans; ¿ Xylitol chewing gum has been demonstrated by other investigators to (1) prevent otitis media (double blind, randomized controlled trial, and (2) maternal consumption prevents dental decay in children at 2 and 5 years of age, even when the children did not chew the gum (level I evidence).

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Section D: Purpose and Objectives

Our overarching hypothesis is that comprehensive primary preterm birth prevention, inclusive of maternal oral health with xylitol chewing gum (the intervention), will reduce the rate of periodontal disease and caries, preterm birth prevalence, and neonatal mortality. We propose two aims to test our hypothesis: ¿ Aim 1 (primary outcome). Our primary aim will be to determine the impact of xylitol gum on the (1) rate of preterm birth <37 and <34 weeks gestation, (2) rate of <2000 gram infants, (3) rate of survival of <2000 gram infants to 30 days, and (4) composite neonatal morbidity of <2000 gram infants at 30 days of age. ¿ Aim 2 (secondary outcome). Xylitol chewing gum has been demonstrated by other investigators to prevent otitis media (double blind, randomized controlled trial (RCT), and maternal consumption prevents dental decay in children up to 5 years of age, even when the children did not chew the gum (RCT). In Malawi, where running water and inadequate dental care are realities of everyday life, we will determine whether use of xylitol gum will decrease the prevalence of (1) periodontal disease, and (2) caries among gravidae.

Section E: Protocol Risks/Subjects

E1. Risk Category

Category 1: Research not involving greater than minimum risk.

E2. Subjects

Gender:
Female

Age:
Adult (18-64 yrs)

Ethnicity:
All Ethnicities

Primary Language:
Chichewe

Groups to be recruited will include:
Both patients and healthy, non-patient, normals

Which if any of the following vulnerable populations will be recruited as subjects?
Pregnant women, Women of child bearing potential

Vulnerable populations require special protections. How will you obtain informed consent, protect subject confidentiality, and prevent undue coercion?
Please see Section J.

E3. Pregnant woman/fetus

Will pregnant women and/or fetuses (as described in 45 CFR 46 Subpart B) be enrolled in the research?
Yes

E4. Neonates

Will neonates of uncertain viability or nonviable neonates (as described in 45 CFR 46 Subpart B) be enrolled in the research?
No

E5. Children

Will children be enrolled in the research?
No

Section F: Design/Procedure

F1. Design

Select one category that most adequately describes your research:
z.r) Randomized, Efficacy Study -- Surgical Techniques/Interventions

Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.
This is a cluster randomized trial. We assessed 12 cluster sites for potential eligibility and excluded 4 sites (around Malawi) because they could not provide reliable delivery data. Of the 8 cluster sites chosen, 4 will be randomly allocated to oral health education and xylitol gum and 4 will be allocated to oral health education and no xylitol gum. The randomization will occur as follows: 1. The first site will be randomized, then computer matched by number of deliveries to the non-intervention site. 2. This process will be repeated in sequence until all 8 sites (4 matched sets) are allocated.

Inclusion Criteria:
The following represent our a priori decided upon inclusion criteria: (1) Enrollment at less than or equal to 20 weeks gestation by best obstetrical estimate; or (2) Enrollment post partum with an anticipated next pregnancy within 18 months; or (3) Enrollment preconception with an anticipated pregnancy within 18 months; and (4) Cognitively aware enough to participate in the study; (5) Greater than or equal to 18 years of age (in Malawi, constitutes a legal adult and capacity to consent for study); (6) Willing to participate in the study; (7) Willing to undergo at least two periodontal exams; (8) Willing to chew 1 piece of xylitol gum for 10 minutes after the morning and evening meal (intervention sites); (9) Anticipating to remain within the region for 18 months.

Exclusion Criteria:
(1) Greater than 20 weeks gestation by best obstetrical estimate; (2) Post partum and not anticipating another pregnancy within 18 months; (3) Preconception and not anticipating another pregnancy within 18 months; (4) Not cognitively aware enough to

participate in the study; (5) Not willing to undergo at least two periodontal exams; (6) Less than 18 years of age; (7) Not willing to chew 1 piece of xylitol gum for 10 minutes after the morning and evening meal (intervention sites); (8) Anticipating a move outside of the region within 18 months.

F2. Procedure

1. Subjects will be recruited by study personnel for potential enrollment during their prenatal visits 2. If enrolled, subjects will be: A) giving medical history/information; B) undergoing a minimum of 2 periodontal exams; (Visit 1 and 2) C) participating in antenatal care; D) chewing xylitol gum (at intervention cluster sites) twice a day following meals; E) undergo delivery (Visit 3) Participants will also be asked to consent to collection of data and potential use of xylitol gum. As previously described, since this product is commercially available over the counter and for the indication of the prevention of dental disease, no IND is necessitated.

Plans for study oversight are as follows: 1. Post-approval, this study will be monitored by the PI and co-PI at BCM in Houston by ensuring that data entry is up to date on a weekly basis. The PI and co-PI will also take regular trips to Malawi to ensure that all study related material is collected and stored according to plan and in compliance with confidentiality requirements. 2. Complaints about the study will be handled by local investigators in Malawi under the guidance of the PI and co-PI at Baylor. 3. Non-compliance on the part of study staff will be address by the PI and co-PI. Study staff will be re-educated on study procedures and confidentiality requirements if indicated, and disciplinary action will be taken if appropriate. 4. Unanticipated Problems Involving Risk to Subjects or Others will be handled by local investigators with immediate notification of BCM PIs and co-PIs. Specifically, if there are unanticipated risks or adverse events, then a significant adverse event report will be filed with the Baylor Institutional Review Board and it will also be reported to the Malawi Ministry of Health for evaluation.

Section G: Sample Size/Data Analysis

G1. Sample Size

How many subjects (or specimens, or charts) will be used in this study?

Local: 10360 Worldwide: 10360

Please indicate why you chose the sample size proposed:

Successful engagement in meaningful global research, and notably a randomized trial, necessitates tremendous up-front leg work and demonstration of feasibility. We have invested three years in preparation for the proposed PPaX trial and are confident in having now parsed down the necessary components suggesting that we can execute the proposed trial on budget and on time, that we should execute the proposed study testing xylitol gum as an intervention, and that it will take a cluster randomization design enrolling a total sample size of 9360 subjects at 8 proposed sites to demonstrate effect size.

We have estimated that a total sample size of 9360 subjects will be sufficient to demonstrate a 33% reduction in the primary outcomes of (1) preterm birth <37 and <34 weeks, and (2) associated neonatal morbidity and mortality based upon our prior work in Malawi. In our study design (where the health center serves as the unit of randomization), we have accounted for a 30% loss to follow up and calculated our per site enrollment to necessitate 1170 subjects at each of 8 sites.

G2. Data Analysis

Provide a description of your plan for data analysis. State the types of comparisons you plan (e.g. comparison of means, comparison of proportions, regressions, analysis of variance). Which is the PRIMARY comparison/analysis? How will the analyses proposed relate to the primary purposes of your study?

Intercluster (between cluster) analysis will include univariate and multivariate analyses analyzing the number of clusters, average cluster size, range of cluster size, rate of preterm birth, rate of neonatal complications, rate of periodontal disease, rate of maternal comorbidities, range and variance of each measure; analysis by intention to treat and by multivariate measures with GEE. Intracluster (per subject, by cluster) analysis will include univariate and multivariate analyses analyzing the number of subjects, average gestational age, rate of preterm birth, rate of neonatal complications, rate of periodontal disease, rate of maternal comorbidities, range and variance of each measure; analysis by intention to treat and by multivariate measures with GEE.

Section H: Potential Risks/Discomforts

H1. Potential Risks/Discomforts

Describe and assess any potential risks/discomforts; (physical, psychological, social, legal, or other) and assess the likelihood and seriousness of such risks:

The potential risks to participants in this study are minor and include the physical risks associated with some of the sample and data collection, risk of psychological distress, and risks to privacy. a.Physical Risks: Intervention: there are no known significant risks to chewing gum b.Psychological Risks: There is no recognized potential risk of psychological distress to the study participants as a result of reflecting on their diagnosis and health history. c.Privacy Risks: There is a small, potential risk of loss of confidentiality. Stringent methods described below will be employed to protect against this risk such that this risk is unlikely.

H2. Data and safety monitoring plan

Do the study activities impart greater than minimal risk to subjects?
No

H3. Coordination of information among sites for multi-site research

Is the BCM Principal Investigator acting as the SPONSOR-INVESTIGATOR for this multi-site research?
Yes

Is BCM the COORDINATING CENTER for this multi-site research?
Yes

If the answer to EITHER of the questions above is "Yes", please complete the following questions:

If this is a multicenter study and the BCM PI is an INVESTIGATOR with responsibilities of SPONSOR or if BCM is the COORDINATING CENTER, describe the management of information among the sites related to participant protections. Your description should include reporting of unanticipated problems, protocol modifications, IRB and/or institutional approvals, and interim results among the sites.

We will follow rigorous procedures to ensure the accuracy, quality, and confidentiality of study data. These procedures include staff training and retraining, close supervision, a Manual of Procedures, and quality control reviews.

Dr. Alan Harris is a PhD trained bioinformatician with a background in anthropology. He has worked in Dr. Aagaard¿s laboratory since 2008, and designed and implemented the on-line database utilized in the seed grant. He will continue to execute the database and assure quality data with inset custom QA QC measures. He will additionally coordinate the database entry and personnel, and complete the biostatistical analyses on rolling data.

When research is conducted in collaboration with outside entities or organizations, the PI must obtain the necessary approvals from those entities. The BCM IRB may request documentation that such approvals have been obtained. Please list and describe the planned sites for this multi-site research for which the BCM PI is either Sponsor-Investigator and/or Coordinating Center. Sites that do not meet the requirements for inclusion in section A6a of the protocol summary and BCM informed consent documents should be listed here.

Letters of support from Malwai, stating that the Ministry of Health supports the project, are attached. The IRB Approval Letter from the Ministry of Health is also attached.

Section I: Potential Benefits

Describe potential benefit(s) to be gained by the individual subject as a result of participating in the planned work.
Potential benefits may include a reduction in preterm birth and an improvement in oral health.

Describe potential benefit(s) to society of the planned work.
If comprehensive oral healthcare and chewing xylitol gum indeed reduces the risk of preterm birth, society would benefit from this knowledge.

Do anticipated benefits outweigh potential risks? Discuss the risk-to-benefit ratio.
The benefits to the participants and to society outweigh the minimal risks of this project.

Section J: Consent Procedures

J1. Waiver of Consent

Will any portion of this research require a waiver of consent and authorization?
No

J1a. Waiver of requirement for written documentation of Consent

Will this research require a waiver of the requirement for written documentation of informed consent?
No

J2. Consent Procedures

Who will recruit subjects for this study?
PI
PI's staff

Describe how research population will be identified, recruitment procedures, any waiting period between informing the prospective participant and obtaining consent, steps taken to minimize the possibility of coercion or undue influence and consent procedures in detail.

The research population will be drawn from eight clinical sites, all in the greater Lilongwe region of Malawi (a 54 km urban-rural region surrounding Lilongwe). Through BIPAI, TCH and BCM have had a continual presence in this region since 2007 and we have been partnered in this region for obstetrical care since 2011.

Women will be recruited in one of two settings: when they present for prenatal care/ at the time of antenatal booking at less than 20 weeks, or postpartum (on the postpartum ward) or preconception with a desire to have another pregnancy in less than 18 months. Women will be approached by trained and experienced community health workers.

Are foreign language consent forms required for this protocol?

Yes

Which of the following ways will you document informed consent in languages other than English?

A full-length informed consent document

J3. Privacy and Intrusiveness

Will the research involve observation or intrusion in situations where the subjects would normally have an expectation of privacy?

No

J4. Children

Will children be enrolled in the research?

No

J5. Neonates

Will non-viable neonates or neonates of uncertain viability be involved in research?

No

J6. Consent Capacity - Adults who lack capacity

Will Adult subjects who lack the capacity to give informed consent be enrolled in the research?

No

J7. Prisoners

Will Prisoners be enrolled in the research?

No

Section K: Research Related Health Information and Confidentiality

Will research data include identifiable subject information?

Yes

Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.

Yes

Specific information concerning alcohol abuse:

No

Specific information concerning drug abuse:

No

Specific information concerning sickle cell anemia:

No

Specific information concerning HIV:

Yes

Specific information concerning psychiatry notes:

No

Demographic information (name, D.O.B., age, gender, race, etc.):

Yes

Full Social Security #:
No

Partial Social Security # (Last four digits):
No

Billing or financial records:
No

Photographs, videotapes, and/or audiotapes of you:
No

Identifiable biospecimens
No

Other:
No

At what institution will the physical research data be kept?
The physical data is maintained at one of two locations. It is either held securely at the BIPAI Baylor Center of Excellence in Lilongwe, Malawi or in the laboratory of Dr. Aagaard at Baylor College of Medicine, Houston Texas (at study completion).

How will such physical research data be secured?
As described in our protocol, data will be under secure storage and locked in the secured records room at the BIPAI Baylor COE or in the laboratory of Dr. Aagaard. The enrollment logs are kept separate from the data to reduce risk of identifying information being with deidentified (subject codes).

At what institution will the electronic research data be kept?
Baylor College of Medicine. Data is uploaded in a completely deidentified manner on a secure server and maintained at Baylor College of Medicine.

Such electronic research data will be secured via BCM IT Services- provided secured network storage of electronic research data (Non-Portable devices only):
Yes

Such electronic research data will be secured via Other:
No

Will there be anyone besides the PI, the study staff, the IRB and the sponsor, who will have access to identifiable research data?
No

Please describe the methods of transmission of any research data (including PHI, sensitive, and non-sensitive data) to sponsors and/or collaborators.
If sent to collaborators, it is only sent with SSL encryption.

Will you obtain a Certificate of Confidentiality for this study?
No

Please further discuss any potential confidentiality issues related to this study.
There are no further potential confidentiality issues.

Section L: Cost/Payment

Delineate clinical procedures from research procedures. Will subject's insurance (or subject) be responsible for research related costs? If so state for which items subject's insurance (or subject) will be responsible (surgery, device, drugs, etc). If appropriate, discuss the availability of financial counseling.
Subjects will not be charged to participate. There are no ensuant costs to the research. Costs of the xylitol gum are covered by the Thrasher Research Fund and will not be incurred to the subjects.

If subjects will be paid (money, gift certificates, coupons, etc.) to participate in this research project, please note the total dollar amount (or dollar value amount) and distribution plan (one payment, pro-rated payment, paid upon completion, etc) of the payment.

Dollar Amount:
0

Distribution Plan:

Subjects will not be paid to participate in this research project.

Section M: Genetics

How would you classify your genetic study?

Discuss the potential for psychological, social, and/or physical harm subsequent to participation in this research. Please discuss, considering the following areas: risks to privacy, confidentiality, insurability, employability, immigration status, paternity status, educational opportunities, or social stigma.

Will subjects be offered any type of genetic education or counseling, and if so, who will provide the education or counseling and under what conditions will it be provided? If there is the possibility that a family's pedigree will be presented or published, please describe how you will protect family member's confidentiality?

Section N: Sample Collection

None

Section O: Drug Studies

Does the research involve the use of ANY drug* or biologic? (*A drug is defined as any substance that is used to elicit a pharmacologic or physiologic response whether it is for treatment or diagnostic purposes)

No

Does the research involve the use of ANY gene transfer agent for human gene transfer research?

No

O1. Current Drugs

Is this study placebo-controlled?

No

Will the research involve a radioactive drug?

No

Section P: Device Studies

Does this research study involve the use of ANY device?

No

Section Q: Consent Form(s)

PPaX Trial (Prevention of Prematurity and Xylitol) ENGLISH CONSENT

Section R: Advertisements

None

Concise and Focused Presentation

You are invited to take part in a research study. Please read this information and feel free to ask any questions before you agree to take part in the study. You have the option not to participate in this study. Whether you participate or not, the care you and your baby receive will not change.

This is a study that is looking at the causes of preterm birth, which is when a baby is born too early. In Malawi, the preterm birth rate is high; it happens in more than 1 of 4 births. When a baby is born too early, it has a higher risk of dying. If it does survive, such babies have problems that can persist the rest of their life, like problems with their lungs (breathing) or problems with their intestines. One thing that increases the risk of a woman delivering a baby too early is having periodontal disease, which is inflammation and disease of the teeth and tooth-gums in the mouth. Some examples of mouth diseases include cavities or teeth-gum inflammation. It is thought that diseases in the mouth may cause preterm birth.

In this study, some pregnancy care clinics will be giving a chewing gum with another version of a sugar, called xylitol. If you participate in this study, whether or not you receive the chewing gum depends on which community health center in Lilongwe that you receive your care at. We don't know if it will be helpful or not to receive the chewing gum for lowering your chance that your baby is born too soo. Therefore, half the health center sites will hand out the gum to enrolled women and half the health center sites will not. If you do not receive the xylitol chewing gum at your site, please do not be worried that we are not giving you something that is known to be helpful in preventing preterm birth. Instead, please understand that the reason we are doing this study is to learn if or if not the xylitol chewing gum will be helpful.

There are no concerning health risks if you choose to participate in this trial. Chewing xylitol gum is not dangerous. There are also no known benefits to participating in this trial, since we encourage all pregnant women to receive good oral health care in pregnancy.

Background

You are invited to take part in a research study. Please read this information and feel free to ask any questions before you agree to take part in the study.

This is a study that is looking at the causes of preterm birth, which is when a baby is born too early. In Malawi, the preterm birth rate is high; it happens in more than 1 of 4 births. When a baby is born too early, it has a higher risk of dying. If it does survive, such babies have problems that can persist the rest of their life, like problems with their lungs (breathing) or problems with their intestines.

One thing that increases the risk of a woman delivering a baby too early is having periodontal disease, which is disease in the mouth. Some examples of mouth diseases include cavities or infections. It is thought that diseases in the mouth may cause preterm birth.

This research study is funded by Thrasher Research Foundation

H-35933- PREVENTION OF PREMATURITY AND XYLITOL (PPAX) TRIAL

Purpose
Chewing gum that contains xylitol, which is a specific kind of gum that has artificial sweetener, decreases periodontal disease.

Because periodontal disease increases the risk of preterm birth and chewing gum that contains xylitol decreases periodontal disease, we are performing this study to assess whether chewing gum with xylitol decreases the rate of preterm birth.

Procedures
The research will be conducted at the following location(s):
Baylor College of Medicine and Baylor College of Medicine Children's Clinical Centers of Excellence Network.

If you agree to participate in this study, the following will happen:

1. We will ask you several questions about your medical history and ask permission to look at your medical chart.
2. We will also ask you to undergo a minimum of two dental exams.
3. (If at a xylitol site): We will also give you a container with 200 pieces of gum. We will ask you to chew this gum for at least 10 minutes twice a day after meals. When you return for your second visit, we will refill your gum.
4. We will ask you to attend a class on oral health.
5. When you come here to deliver, we will collect information about your delivery.

Clinically Relevant Research Results
The results generated from this research study are not expected to have any clinical relevance to you.

Sharing and Future Research Studies with Identifiable Private Information
Information that identifies you may be removed from your identifiable private information collected as part of this research, and after such removal, your information may be used for future research studies or distributed to another investigator for future research studies without additional consent/authorization from you.

Research related health information
Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you sign this document, you give permission to people who give medical care and ensure quality from Baylor College of Medicine and Baylor College of Medicine Children's Clinical Centers of Excellence Network to use or disclose (release) your health information that identifies you for the research study described in this document.

The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.

- Specific information concerning HIV
- Demographic information (name, D.O.B., age, gender, race, etc.)

The health information listed above may be used by and or disclosed (released) to researchers, their staff and their collaborators on this research project, the Institutional Review Board, Baylor College of Medicine, Baylor College of Medicine Children's Clinical Centers of Excellence Network, and THRASHER RESEARCH FUND and their representatives.

Use or Disclosure Required by Law

Your health information will be used or disclosed when required by law.

Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability and conducting public health surveillance, investigations or interventions.

Baylor College of Medicine and Baylor College of Medicine Children's Clinical Centers of Excellence Network are required by law to protect your health information. By signing this document, you authorize Baylor College of Medicine and Baylor College of Medicine Children's Clinical Centers of Excellence Network to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

Please note that the research does not involve treatment. Baylor College of Medicine and Baylor College of Medicine Children's Clinical Centers of Excellence Network may not condition (withhold or refuse) treating you on whether you sign this Authorization.

Please note that you may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers, their staff and their collaborators on this research project, the Institutional Review Board, THRASHER RESEARCH FUND and their representatives, regulatory agencies such as the U.S. Department of Health and Human Services, Baylor College of Medicine, and Baylor College of Medicine Children's Clinical Centers of Excellence Network may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. If you revoke this Authorization, you may no longer be allowed to participate in the research described in this Authorization.

To revoke this Authorization, you must write to: Dr. Kjersti Aagaard
BIPAI Baylor COE
Lilongwe, Malawi

This authorization does not have an expiration date. If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Potential Risks and Discomforts
The possible risks of this study are small.
There are no known significant risks to chewing gum.
There is a small risk of loss of confidentiality, meaning that your private information would not be private. We will keep all paper information locked in a cabinet in a locked room. Any information on a computer will be encrypted.

Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

Potential Benefits
The benefits of participating in this study may be: a reduction in the risk of preterm birth.. However, you may receive no benefit from participating.

Alternatives
You may choose to not participate in this study.

Subject Costs and Payments
You will not be asked to pay any costs related to this research.

You will not be paid for taking part in this study.

Subject's Rights
Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The investigator, KJERSTI AAGAARD, and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: KJERSTI MARIE AAGAARD at 713-798-8467 during the day and after hours.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is (713) 798-6970. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Parent	Date
Investigator or Designee Obtaining Consent	Date
Witness (if applicable)	Date
Translator (if applicable)	Date

CONSENT FORM

Prevention of Prematurity and Xylitol (PPaX) Trial Chichewa Consent

Background

Mukupemphedwa kuti mutenge nawo mbali mukafukufuku. Chonde werengani uthengawu ndipo mukhale omasuka kufunsa mafunsa ena aliwonse musanavomereze kutenga nawo mbali mukafukufuku.

Uyu ndi kafukufuku amene akuona zifukwa zimene zimayambitsa kubadwa kwa mwana nthawi isanakwane, komwe kuli kubadwa kwa mwana mwachangu nthawi isanakwane. Kumalawi, chiwerengero cha ana obadwa masiku osakwana ndi chokwera; zimachitika moposera mwana mmodzi pa ana anayi aliwonse obadwa. Mwana akabadwa msanga masiku asanakwane, amakhala ndi mpata waukulu wakuti akhoza kumwalira, ngati angakhale ndi moyo, ana otere amakhala ndi mavuto oti akhoza kumangochitika moyo wawo onse, monga mavuto a m'mapapo, (kupuma) kapena mavuto okhudza matumbo awo.

Chinthu chimodzi chimene chimaonjezera mpata wa amayi kubereka mwana msanga masiku asanakwane ndi kukhala ndi matenda a periodontal, amene ali matenda a mkamwa. Zina mwa zitsanzo za matenda a mkamwa ndi kubooka kwa mano. Matenda a mkamwa amaganizidwa kuti akhoza kuyambitsa kubadwa kwa mwana msanga masiku asanakwane. Kafukufukuyu akuthandizidwa pa za chuma ndi bungwe la Thrasher Research Foundation

Cholinga

Kutafuna chingamu chimene chili ndi xylitol, chimene chili chingamu chapadera chokhala ndi shuga ochita kuyika, kumamachepetsa matenda a mkamwa.

Chifukwa chakuti matenda a mkamwa a periodontal amaonjezera mpata obadzwitsa mwana masiku osakwana ndipo kuti kutafuna chingamu chokhala ndi xylitol kumachepetsa matenda a mkamwa a periodontal, tikupanga kafukufukuyu kuti tifufuze ngati kutafuna chingamu chokhala ndi xylitol kumachepetsa chiwerengero cha ana obadwa masiku asanakwane.

Zochitika

Kafukufuku adzachitikira m'madela awa: ku Baylor College of Medicine ku zipatala za ana za kuno ku Malawi ndi madela ozungulira.

Ngati muvomereze kutenga nawo mbali mukafukufuku, zidzachitike ndi izi;

1. Tidzakufunsani mafunso angapo okhudza mbiri yanu ya zaumoyo komanso kupempha chilolezo chakuti tiwelenge zolembalemba za m'mbuku lanu la kuchipatala.
2. Tidzakupemphaninso kuti muyesedwe maulendo awiri ngati muli ndi matenda okhudza mkamwa
3. (Ngati muli pa malo amene chingamu cha xylitol chikuperekedwera) tidzakupatsani contena yokhala ndi chingamu 200. Tidzakupemphani kuti mutafune chingamuchi kwa nthawi yokwana mphindi khumi (10 minutes) kawiri pa tsiku mukatha kudya. Mukabweranso ku ulendo wanu wa chiwiri, tidzakupatsani chingamu chanu china.
4. Tidzakupemphani kuti muphunzire kalasi ya maphunziro okhudza ukhondo wa mkamwa.
5. Mukabwera kuno kudzabereka, tidzatenga uthenga okhudza momwe mwaberekera.

CONSENT FORM

Prevention of Prematurity and Xylitol (PPaX) Trial Chichewa Consent

Uthenga okhudza kafukufuku wa zaumoyo

Mukhoza kuwona komanso kutenga chikalata cha uthenga wanu wa kafukufuku wa zaumoyo. Dokotala wanu wa kafukufuku akhoza kukupatsani mbali ya uthenga wanu pamene kafukufuku akupitilira ndi kumalizitsa uthenga onse ku mapeto a kafukufuku.

Zovuta ndi zosowetsa mtendere zomwe zingakhalepo

Zovuta zomwe zingakhalepo zokhudza kafukufuyu ndi zochepa.

Palibe zovuta zodziwika zokhudza kutafuna chingamu.

Pali vuto pang'ono lakuti chinsinsi chikhoza kuchepa, kutanthauza kuti uthenga wachinsinsi okhudza inu sungakhalenso wachinsinsi. Tidzasunga uthenga onse olembedwa pa pepala mu kabati yokiya muchipinda chokiya. Uthenga uliwonse umene uli mu makina a kompyuta udzakhala otetezedwa ndi nambala yolowera.

Ogwira ntchito mukafukufuku adzakudziwitsani pa nthawi yoyenera za uthenga uliwonse umene ungasunthe chidwi chanu chokhala mukafukufuku.

Phindu lomwe lingakhalepo

Phindu lomwe lingakhalepo potenga nawo mbali mukafukufuku likhoza kukhala: kuchepa kwa kubereka mwana amene sanakwane masiku. Komabe mukhoza osapeza phindu potenga nawo mbali mukafukufuku

Njira zina

Mukhoza kusankha osatenga nawo mbali mukafukufuku

Malipiro komanso zolipira kwa otenga nawo mbali.

Simudzapemphedwa kulipira malipilo ena aliwonse okhudza kafukufuyu.

Simudzalipilidwa kamba kotenga nawo mbali mukafukufukuyu.

Ufulu wa otenga nawo mbali

Kusayina yanu pa chikalata cha chivomerezochi ikukutanthauza kuti mwalandira uthenga okhudza kafukufukuyu ndipo kuti mukuvomereza modzipereka nokha kutenga nawo mbali mukafukufukuyu.

CONSENT FORM

Prevention of Prematurity and Xylitol (PPaX) Trial Chichewa Consent

Mupatsidwa chikalata chosainidwa ngati chomwechi kuti mukasunge. Simukutaya ufulu wanu uliwonse posayina chikalatachi. Ngakhale pamene mwasayina chikalatachi, mukhoza kusintha maganizo anu nthawi ina iliyonse. Chonde kumanani ndi ogwira ntchito mukafukufuku ngati mutaganiza zosiya kafukufukuyu.

Ngati mutaganiza kusatenga nawo mbali mukafukufukuyu kapena ngati mutaganiza zosiya kutenga nawo mbali kutsogoloku, phindu komanso chithandizo cha kwa inu zidzakhala chimodzimodzi monga tinakambira kale zokhudza kafukufukuyu. Simudzaluza phindu, chithandizo kapena ufulu.

Uthenga wanu wa zaumoyo

Tikhoza kumatenga uthenga okhudza zaumoyo umene ukhoza kulumikizana ndi inu (uthenga wa zaumoyo otetezedwa) uthenga wa zaumoyo otetezedwawu ukhoza kukhala ndi dzina lanu, komwe mukukhala, namabla ya chitetezo yanu kapena kukhala ndi chinachake chimene chikhoza kukuzindikiritsani. Malamulo a dziko lonse akufuna ife titenge chilolezo chogwiritsa ntchito uthenga wanu otetezedwa wa zaumoyo pa kafukufukuyu. Kusayina kwanu pa chikalatachi kukutanthauza kuti mukutipatsa ife chilolezo kugwiritsa ntchto uthenga wanu wa zaumoyo otetezedwa mukafukufukuyu.

Ngati mutaganiza zotenga nawo mbali mukafukufuku, uthenga wanu wa zaumoyo otetezedwa superekedwa pokhapokha monga momwe lamulo limalolera kapenga monga zafotokozeredwa mu chikalatachi. Aliyense amene akugwiritsa nthcito uthenga wanu wa zaumoyo otetezedwa akuyenera kusunga uthengawu mwachinsinsi. Zotsatira zakafukufukuyu zikhoza kusindikizidwa. Komabe, simudzadziwika ndi dzina lanu.

Anthu amene amapereka chithandizo cha zaumoyo komanso kuwonetsetsa kuti zikuchitika mwapamwamba ndi dongosolo la bwino ochoka ku malo onse amene kafukufuku akuchitikira, amene akuthandiza pa za chuma amene alembedwa pa gawo la pamwamba, oyimilira a othandiza pa chuma, komanso mabungwe amene amawunikira monga bungwe loyang'anira za umoyo komanso kutumikira anth (U.S. Department of Health and Human Services), adzaloledwa kuwona zigawo za zolembalemba za umoyo wanu komanso zofufuza zokhudza kafukufukuyu. Chifukwa cha kufunika kwa ofufuza komanso ogwira ntchito mukafukufuku pa kupereka uthenga ku mabungwe amenewa, sitingatsimikize chinsinsi chotheratu.

Anthu amene alembedwa pamwabawa akhoza kuwona uthenga wanu nthawi iliyonse imene angafune, ngakhale kafukufuku atatha.

Ngati mwaganiza zosiya kutenga nawo mbali mukafukufuku kapena ngati mwachotsedwa mukafukufuku, mukhoza kupanga chiganizo chakuti uthenga umene umakuzindikuritsani usagwiritsidwenso ntchito mukafukufukuyu. Awuzeni ogwira ntchito mukafukufuku kuti adziwe za chiganizo chimenechi, ndipo adzakupatsani keyala ya ofufuza wankulu kuti muwadziwitse polemba kalata. Ofufuza wankulu adzalemekeza chiganizo chanu pokhapokha ngati kusagwiritsa nthcito uthenga wa zaumoyo okuzindikiritsani ungasokoneze ubwino kapena kupangidwa kwa pamwamba kwa kafukufuku.

Afufuzi akulu, PETER KAZEMBE, BERTHA BANDA, KAPENA KJERSTI MARIE AAGAARD, Ndi/ Kapena wina amene amusankha olowa m'malo mwao adzayesetsa kuyankha mafunso anu onse. Ngati muli ndi mafunso kapena madandaulo, kapena mukufuna kufotokoza za ngozi yokhudza kafukufuku, mukhoza kuyankhula ndi m'modzi wa ogwira ntchito mukafukufuku.

CONSENT FORM

Prevention of Prematurity and Xylitol (PPaX) Trial Chichewa Consent

Kusaina chikalata cha chivomerezochi zikutanthauza kuti mwawerenga chikalatachi (kapena chinawerengedwa kwa inu), kuti mafunso anu ayankhidwa moti inuyo mwakhutitsidwa, komanso kuti mukuvomereza mofuna nokha kutenga nawo mbali mukafukufukuyu. Mulandira chikalata chosayina kale cha ngati chomwechi

Sayini Tsiku

Afufuzu kapena oyimira m'malo mwawo Tsiku

Mboni (ngati Kungafunike) Tsiku

Otanthauzira (ngati Kungafunike) Tsiku