START CENTER
STRATEGIC ANALYSIS,
RESEARCH & TRAINING CENTER

A LANDSCAPE ASSESSMENT OF ONGOING TRIALS FOR EED: EXECUTIVE SUMMARY REPORT

UNIVERSITY OF WASHINGTON STRATEGIC ANALYSIS, RESEARCH, & TRAINING (START) CENTER

REPORT TO THE BILL AND MELINDA GATES FOUNDATION

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OVERVIEW

The University of Washington (UW) Department of Global Health Strategic Analysis and Research Training Program (START) team conducted a landscape assessment of the published literature to identify interventional studies for Environmental Enteric Dysfunction (EED) in December 2015. This report reviews ongoing interventional trials for EED identified from ClinicalTrials.gov and key informant interviews.

BACKGROUND

EED is a condition in which repeated enteropathogen infection leads to chronic gut inflammation and increased intestinal permeability. The result is malabsorption of nutrients and thus slowed linear growth (i.e. stunting). Additionally, there are links between EED and decreased cognitive development. Given the increased morbidity associated with EED and its impact on child growth, the Enteric and Diarrheal Diseases (EDD) and Discovery and Translational Sciences (DT&S) teams at the Bill and Melinda Gates Foundation (BMGF) are investing in studies to further define EED, to understand the causal pathways of pathology, its associated morbidities, and to identify potential interventions.

In September of 2015, BMGF requested a landscape assessment of the study designs, endpoints and results of completed and ongoing trials with EED-related endpoints to help inform decisions on future interventional trials for EED. Following discussions with BMGF, Phase1a reviewed the published literature from completed trials. This report summarizes findings from Phase Ib, a review of ongoing interventional trials for EED.

PHASE IB INTRODUCTION: ONGOING INTERVENTIONAL TRIALS

Phase Ib synthesizes 23 ongoing interventional studies that implement EED biomarkers and anthropometric measures, provides current themes among investigators, and explores possible future directions. “Appendix 4: Ongoing Trials for EED” is a catalogue of the following key aspects of these studies:

- Intervention(s)
- Primary and secondary endpoints and outcomes
- PI(s), title, & geography
- Study design
- Age group
- Enrollment
- Project start and end date

METHODS

The search strategy focused on identifying interventions utilizing EED terms along with terms for stunting in Clinicaltrials.gov. The search terms were:

- (environmental enteric dysfunction OR environmental enteropathy OR EED OR tropical enteropathy OR enteric dysfunction) OR ("growth faltering" OR "stunting")

After applying an "interventional" filter, 154 study titles were reviewed for relevant biomarkers or EED-specific terms. Two reviewers utilized a split-review consensus-driven approach. Studies were identified for inclusion on the basis of relevance and compliance with exclusion and inclusion criteria outlined in Phase 1a (see Appendix 1). Phase 1b also included studies without EED biomarkers as well as studies utilizing microbiota endpoints if consensus was reached regarding relevance to EED. Studies previously included in Phase Ia or completed prior to 2013 were excluded.

UW START also conducted a series of interviews with subject matter experts working on current and past EED interventional trials. The team then implemented a snowball strategy of referrals from these experts to identify additional research not captured in the review of current clinical trials. The interviewees are listed in Appendix 3.

RESULTS

Our search yielded 18 ongoing trials reported in ClinicalTrials.gov. Our subject matter expert interviews produced five additional trials with either primary or secondary outcomes related to EED. These 23 studies were categorized according to the intervention strategy deployed and are heterogeneous with regard to: specific intervention; amount, type, and frequency of collection of outcome measures; geography; and age group. Categories include anti-pathogen interventions; combination interventions; water, sanitation and hygiene interventions; micronutrient interventions; probiotics; supplemental nutrition therapies; and nutrition education. Anti-pathogen interventions include antibiotic and anthelmintic therapies that target infection and parasitic infestation. Hygiene and sanitation interventions target improvements to water quality, environmental modifications designed to reduce exposure to waste, and behavioral practices to improve hygiene. Micronutrients, probiotics and supplemental nutrition therapies include complementary feeding, glutamine supplementation, *Lactobacillus reuteri*, or micronutrients (e.g zinc) to improve gut function. The combination category includes studies in which two or more interventions were tested. Lastly, the nutrition education category includes one study implementing a nutrition education program for mothers.

AGE

The majority of studies (19) have age eligibility criteria for children under-five. However, the upper age limits for this eligibility are diverse and include 12-months, 18-months, 24-months, 36-months, and 60-months. Four studies are looking to recruit or have already recruited mothers with the intention to follow children after birth.

GEOGRAPHY

All ongoing studies are conducted in LMICs with one multi-country study, 13 trials conducted in sub-Saharan Africa, six in Asia, and three in Latin America.

OUTCOME MEASUREMENTS

Overall, six of the studies test either an ambiguous or extremely mixed set of biomarkers for EED. Of these, three demonstrate a potential trend through the inclusion of neopterin, myeloperoxidase, and alpha-1 anti-trypsin as EED biomarkers. Five studies have a microbiota-related outcome. Three studies have immune-related biomarkers as the primary or only marker, such as C-reactive protein. Seven studies are using L:M ratio as the primary or priority EED-related biomarker. Of the seven studies that identify an EED biomarker as a primary outcome, six of these use lactulose and mannitol measurements. For the 14 studies with non-biomarker primary outcomes, popular measures include incidence and prevalence of diarrheal disease, anthropometric measures, and mortality/morbidity. Two studies also examine cognitive and developmental outcomes. Three studies examine both stunting-related measures and diarrhea and two look at stunting and mortality as primary outcomes. None of the studies include growth velocity as an outcome measure.

INTERVENTIONS

Ongoing studies are summarized in the following sections by intervention category. These sections list the study titles included in the section and describe the rationale behind each type of intervention. They also highlight the ages of eligibility, expected completion dates, and select details in order to synthesize and complement the information in the table in Appendix 4. Studies are numbered in the table and linked to the respective titles.

WATER, HYGIENE, AND SANITATION (4, 5, 6, 21)

4) SHINE Sanitation, Hygiene, Infant Nutrition Efficacy Project
5) WASH Benefits Kenya
6) WASH Benefits Bangladesh
21) Automatic Chlorination and Child Health in Urban Bangladesh

A causal model wherein multiple and potentially overlapping exposures are responsible for childhood stunting via the EED pathway provides the premise for current sanitation interventions. Poor sanitation, hygiene, and water quality and scarcity facilitate the ingestion of potentially enteropathogenic fecal microbes that are considered to be the primary cause of EED. In addition to the primary rationale, three of the four studies included supplemental nutrition, reflecting that undernourished children are immunocompromised and are therefore more susceptible to frequent and prolonged enteric infection than well-nourished children (1, 2). The rationale for the Sanitation, Hygiene, Infant Nutrition Efficacy Project (SHINE) study also suggests repeated exposure to mycotoxins found in staple foods may result in the intestinal damage characteristic of EED, advancing an alternative nutrition driven EED-mediated pathway to stunting (3).

Three of the four studies identified children through enrollment of pregnant women, while the Automatic Chlorination and Child Health study in Bangladesh selected households with children under 5 years. WASH Benefits Bangladesh is the study ending earliest, with an anticipated completion in April of 2016. The SHINE trial and its associated nested study looking at maternal EED will not be complete until December and May of 2017, respectively.

The SHINE trial explores the biological causal pathway of EED through a sub-study comparing biomarkers of EED collected from stool samples of 1,000 HIV-unexposed infants and all consenting HIV-exposed infants. Stool specimens during diarrheal episodes will also be collected from a cohort of 800 EED infants reaching 3 months of age between June 2015-March 2017, these samples will be evaluated for the presence of diarrheal pathogens.

COMBINATION INTERVENTIONS (2, 3)

2) Combined Package of Interventions for Environmental Enteropathy
3) Water-Based Zinc Efficacy Trial in Beninese School Children

Combination interventions include interventions wherein at least one experimental arm comprises of two or more interventions from unique intervention categories. The Combined Package of Interventions for Environmental Enteropathy study (Combined Package) combines an anti-pathogen, micronutrient and multiple micronutrients. The Water-Based Zinc (Water-Based Zn) Efficacy Trial combines water filtration and zinc supplementation.

While both studies include measures of EED biomarkers, only Combined Package includes an EED biomarker as a primary outcome. Water-Based Zn includes a greater and more diverse set of EED biomarkers and anthropometric measures in the secondary outcomes but is only powered to observe changes in serum zinc concentration. Sample sizes in these studies are comparable: Combined Package enrolled 253 participants and Water-based Zn has 278 participants. These studies share some similarities and distinctions in the special populations excluded from the study. Combined Package excludes children with Severe Acute Malnutrition (SAM) and Water-Based Zn excludes children with severe anemia.

Age ranges sampled in both studies also vary considerably with children age 6-10 years representing the eligible children in Water-Based Zn and children age 12-35 months in Combined Package. Both trials have reached primary completion; the final data collection date for the primary outcome measure was April 2015 in Combined Package and July 2013 for Water-Based Zn.

ANTI-PATHOGEN (1, 22, 23)

1) The Impact of Anthelmintic Treatment on the Incidence of Diarrheal Disease in Vietnamese School Children
22) Toto Bora: Azithromycin (AZM) to Prevent Post-discharge Morbidity and Mortality in Kenyan Children

23) ABCD Trial

Three studies in our review test or will test Azithromycin, Ciprofloxacin, or Albendazole to address the potential pathogenic genesis and relationship to EED through bacterial infection or helminthic infestations. The ABCD trial and Toto Bora trials each evaluate potential improvements to morbidity and growth faltering conferred by Azithromycin or Ciprofloxacin therapies in children. The Impact of Anthelmintic Treatment on the Incidence of Diarrheal Disease in Vietnamese School Children trial includes the oldest age range present for children, with eligibility extending to children aged 6-15 years. This study is slated to complete data collection on the primary outcome in August 2017.

The ABCD trial is a multi-site study occurring across three South Asian countries and four Sub-Saharan African countries and represents the largest study included in the whole set of ongoing trials with approximately 15,000 study subjects projected to enroll. Twenty five percent of participants and one child under five years from the same household will be randomly selected for stool samples/rectal swabs.

The Toto Bora trial examines the potential of Azithromycin prophylactic treatment to prevent post-discharge morbidity and mortality in Kenyan children ranging from 1-59 months of age. A random subset of 300 children, 150 per arm, will comprise the Enteric Function Cohort. These children will be sampled to study measures of gut function using a triplicate of stool biomarkers, neopterin (NEO), alpha-anti-trypsin (AAT), myeloperoxidase (MPO).

The Toto Bora trial is expected to conclude in February 2020, and the ABCD trial end date is estimated to conclude August 2020.

MICRONUTRIENTS (MNS) (7, 8, 9, 10)

7) Lao Zinc Study: Effects of Two Forms of Daily Preventive Zinc Versus Therapeutic Zinc Supplementation
8) Supplementing Maternal and Infant Diet with High-Energy, Micronutrient Fortified Lipid-based Nutrient Supplements (LNS)
9) Complementary Food Supplements for Reducing Childhood Undernutrition
10) Zinc Resistant Starch Project

Four studies in our review include interventions implementing micronutrient (MN) therapies. This is the second most popular intervention category and may reflect enthusiasm around evidence that mucosal and villous damage may be improved by alleviating micronutrient deficiencies (4). The four studies included in this category used a number of approaches to address nutritional deficiencies including food, zinc, multiple micronutrients (MMNs) and iron with folate supplements.

The Lao Zinc Study includes the second largest sample size in this category, with 3,400 participants. The Zinc Resistant Starch Project includes provides a sample of 20 mothers with Zinc micronutrient therapy during complementary feeding. Complementary Food Supplements for Reducing Childhood Undernutrition is the only study in this category to include an outcome related to cognitive development. It also collects EED biomarkers, in addition to anthropometric measures of 5,449 participants and is reported to have completed data collection of primary outcomes in November 2014.

Supplementing Maternal and Infant Diet With High-energy, Micronutrient Fortified Lipid-based Nutrient Supplements (LNS) takes a unique approach in measuring vaginal microbiota markers in mothers. This study compares LNS treatment to MMNs and iron with folate treatment groups. In August 2011, the study was revised to include a substudy on the development of the intestinal microbiome of infants. Investigators aim to identify predictors and any associations between the microbiome and growth as well as other health outcomes. During this time, funding constraints drove investigators to reduce sample size from 2,400 participants to 1,400, with 1,391 participants ultimately enrolled. Data collection for the primary outcomes—birthweight, height, and LAZ, are reported to have concluded in April 2015.

PROBIOTICS (12, 13, 14)

12) Safety of Lactobacillus Reuteri in Healthy Children Aged 2-24 Months
13) Safety of Lactobacillus Reuteri in Healthy Children Ages 2 to 5 Years in Peru
14) Novel Diagnostics and Probiotics to Improve Management of Paediatric Acute Gastroenteritis

Probiotics aim to treat the pathogenic causes of EED by introducing benign species to compete with bacteria with more deleterious effects. Our review includes studies with interventions including probiotic therapies of *Lactobacillus reuteri.* Phase I of *L. reuteri* for Pediatric Diarrhea in Peru: Growth, Enteropathy, and Microbiota (PRIDEC Peru) targets 60 children ages 2-24 months old. A parallel study examines the same treatment in children ages 2-5 years. The studies are each reported to have completed data collection on the primary outcome as of December 2015 and June 2015, respectively. PRIDEC Peru Phase II is planned but has not yet enrolled and no further information is currently available.

Whereas the other two studies in this category sample from relatively healthy children from the community, Novel Diagnostics and Probiotics to Improve Management of Pediatric Acute Gastroenteritis is a pilot trial administering probiotic therapy to children hospitalized for viral gastroenteritis. Investigators seek to examine if a *L. reuteri* treatment will reduce the duration of diarrhea in these children. The study is reported to have completed as of March 2016.

SUPPLEMENTAL NUTRITION THERAPIES (15, 16, 17, 18, 19, 20)

15) The Impact of Legumes vs Corn-soy Flour on Environmental Enteric Dysfunction in Rural Malawian Children 1-3 Year Olds
16) The Impact of Legumes vs Corn-soy Flour on Environmental Enteric Dysfunction in Rural Malawian Children 6-11 Months
17) Intervention and Mechanisms of Alanyl-Glutamine for Inflammation, Nutrition, and Enteropathy (IMAGINE)
18) ω3 LCPUFAs for Healthy Growth and Development of Infants and Young Children in Southwest Ethiopia
19) Bangladesh Environmental Enteric Dysfunction (BEED)
20) Randomized, double blind, placebo controlled trial comparing the impact of lactoferrin and lysozyme supplementation versus placebo in the treatment of sub-clinical environmental enteropathy in rural Malawian children

The most popular intervention category represented in our review includes studies whose intervention strategy uses supplemental nutrition therapies also theorized to repair damaged tissue and mucosal surfaces. Of the six studies in this category, three provide nutritional therapies in the form of foods and three detail specific supplements used including lysozyme and lactoferrin; ω3 LCPUFAs; and Alanyl-Glutamine.

This category also includes the most geographically diverse group of studies situated in South Asia, Sub-Saharan Africa, and South America. Sample sizes range from 140 - 1,500 participants for outcome measures related to EED. The Intervention and Mechanisms of Alanyl-Glutamine for Inflammation, Nutrition, and Enteropathy (IMAGINE) study includes children ages 2 months-5 years old and is the only study to use graded dosage of a single treatment in our review. To date, only the IMAGINE, ω3 LCPUFAs for Healthy Growth and Development of Infants and Young Children in Southwest Ethiopia, The Impact of Legumes vs Corn-soy Flour on Environmental Enteric Dysfunction in Rural Malawian Children 1-3 Year Olds, and The Impact of Legumes vs Corn-soy Flour on Environmental Enteric Dysfunction in Rural Malawian Children 6-11 Year Olds studies have reached their expected completion dates for primary data collection. The Bangladesh Environmental Enteric Dysfunction trial (BEED) is the only study included in our review to use histological samples from endoscopy of 20% of participants, adults and children, to confirm EED and is expected to end in December 2019.

NUTRITION EDUCATION (11)

11) Improving the Nutrition Status of Infants in South-Western Uganda

Only one study in our review included a purely behavioral intervention. Improving the Nutrition Status of Infants in Southwestern Uganda seeks to address growth restriction and compromised cognitive development due to undernutrition. Mothers of 510 infants aged 6-36 months are enrolled in a nutrition education program to determine if increased knowledge improves poor nutrition when nutrient intake is not exclusively attributable to a lack of resources.

Primary outcomes include are a change in the prevalence of stunting and a change in the Bayley Mental Development Index score. The trial will complete data collection of primary outcomes in July 2016.

PRELIMINARY FINDINGS

Many of the studies identified from speaking with subject matter experts did not have preliminary findings available due to the nature of their double-blinded design. However, two experts spoke on information that was available regarding their respective studies. These results are subject to change as data and analyses are ongoing.

> "SO MANY RCTS OF WASH HAVE FAILED, NOT BECAUSE OF THE THEORY BUT BECAUSE THE PROGRAM NEVER GOT IMPLEMENTED OR IMPLEMENTED AS DESIGNED"

Investigators in SHINE reported high fidelity and uptake to the WASH interventions. Jean Humphrey emphasized the importance of this as "so many RCTs of WASH have failed, not because of the theory but because the program never got implemented or implemented as designed."

Preliminary findings of WASH Bangladesh demonstrate improved EED markers at midline compared to baseline measurements. EED markers were also found to have lower levels than observed in MAL-ED findings, suggesting a potential causal effect of improved sanitation on growth and development. WASH Bangladesh is scheduled to have completed data collection on EED biomarkers in March 2016 with analysis expected to conclude in 2016. The Kenya WASH Benefits trial is expected to conclude in 2017.

The primary outcome analyses are complete in the IMAGINE study. The main finding demonstrated only one significant result, a decline in L:M ratio for the middle dosing level, 6 g/day. The result countered an expected dose-response trend. Since the groups were heterogeneous in terms of age and the dose was standard by group, the investigators are planning to conduct an exploratory analysis with weight-based dosing in order to further probe any dose-response relationship.

FUTURE DIRECTIONS

PATHWAYS

The majority of key informants agreed that EED is a non-precisely defined chronic condition with a potentially complex etiological mechanism or set of mechanisms. Steve Luby acknowledged that there is no silver bullet in this situation. Jay Berkley reflected these comments with the added insight that the perspective is in what the biggest impact would be to work on first. Bill Petri reviewed the PROVIDE study where malnutrition explained about half of the variation in EED and proclaimed that there were three independent pathways on which to intervene, malnutrition, vaccination, and WASH.

We define these approaches to intervention as "Repair, Prevent, and Regulate." Recognizing that each intervention could potentially act in two or more of the ways outlined in this framework, we categorize complementary food,

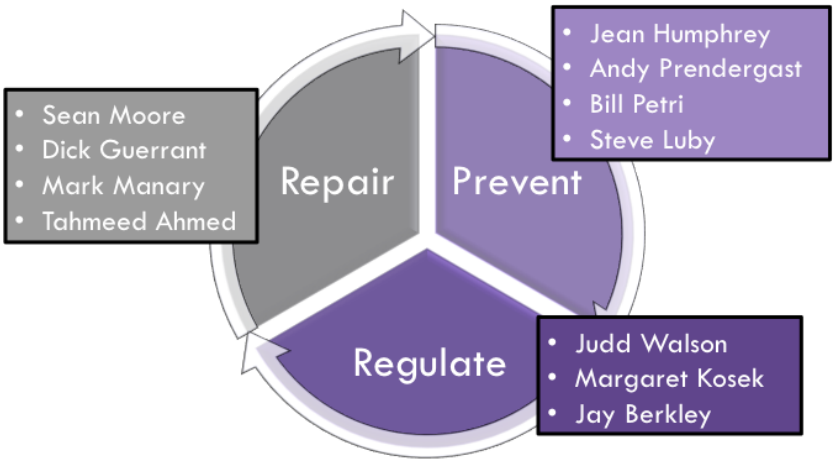

FIGURE 1

supplements such as glutamine, and micronutrients such as zinc into the repair category for their potential to aid in mucosal repair and epithelial cell replication. Prevention includes WASH interventions as well as innovative ideas for vaccinations of mothers. Regulate encompasses the pathogenic balance once an organism is in the body and includes pre/probiotics, anti-pathogens, and anti-inflammatories.

A summary of subject matter expert perspectives as revealed either through their current research or additional comments (if they did not have a current study) is presented in Figure 1.

SAM

A few of the subject matter experts expressed their uncertainty or disagreement around the link between severe acute malnutrition and EED. Tahmeed Ahmed in describing his perspective stated that he believed it was separate but would be evaluating that belief in his own upcoming study, BEED.

The extreme and acute nature of SAM presents pediatric enteropathic patients within clinical settings while potentially straying too far from an underlying chronic condition of EED. One subject matter expert described why he does not include children with SAM in his studies, "SAM is very treatable already, and there are too many other things going on with these kids," inferring that the very nature of being so ill makes them incomparable to children with EED.

> "SAM IS VERY TREATABLE ALREADY, AND THERE ARE TOO MANY OTHER THINGS GOING ON WITH THESE KIDS"

Andy Prendergast offered a counterpoint in describing his observational study HOPE-SAM, a study in Zambia and Zimbabwe in a population of children afflicted with HIV and malaria, stating that the endoscopy and EED biomarkers collected would perhaps shed light on an underlying chronic condition and its relationship to these acute issues.

CONCEPTUAL STUDIES

Several subject matter experts provided some information on conceptual studies they were either in discussions with individuals about or would like to do in the future. A couple of interviews also elicited additional responses on where opportunities are to approach EED from other fields of study. These are listed below.

IN DISCUSSIONS AND THEORETICAL NEXT STEPS

A number of key subject matter experts provided information on studies that are either in discussions with various industries and entities or are ideas between collaborators in very nascent stages. One expert spoke of the potential of ogliosaccharides to be added to formula for infants as a prebiotic supplement. As well, he spoke of the interest in using treatments that are currently used for treatment in pediatric short-cut syndrome, GLP2 – teglugliatides. Another expert mentioned continued interest but no current funding stream for small molecules, "ODS", which could mediate the inflammatory response responsible for stunting.

Additionally, many experts stated their opinions on potential future approaches for interventional studies examining EED, including:

- "Try other SIBO treatments and give in a short course and see if it works and is safe. Longer way down the line is steroids but need safer drugs."
- "Tryptophan OR glutanyl-trytophan, Zinc with Vit A, then Zinc with Arginine; lactoferrin"
- Maternal vaccination

CROSS-FERTILIZATION AND INNOVATIVE IDEAS

Several other ideas were elicited from interviews that could serve as a potential guide for future interventional work:

- Performing a natural experiment in individuals in mass migration from the Middle East and Asia to Europe
- Borrowing from other scientific fields like oncology may yield information about how to approach the microbiome
- ApoE4 and work done in Alzheimer's could be promising for studying the cognitive effects of EED

DISCUSSION

The variety of perspectives and ongoing trials is indicative of both the complexity of this chronic condition, as well as challenges in defining it. Specific questions arose during interviews on the topics of SAM and of the role that the microbiome might play in this condition. The heterogeneity of these ongoing trials reflects the potential need for future and continued exploration into biomarkers, appropriate ages for an intervention, safety and efficacy trials of adult treatments for vulnerable children, and expanded strategies to examine treatments for other bowel- and cognitive-related diseases and approaches from other specialties to better regulate chronic conditions.

STRENGTHS AND LIMITATIONS

STRENGTHS

Strengths of the UW START team's approach include:

- Review of a large number of ongoing trials from Clinicaltrials.gov by including growth-related terms
- Interviews with 11 individuals considered field experts, who often cross-referenced each other regarding investigators studying EED interventions
- Interviews provided some updates and context to database searches

LIMITATIONS

- Single database of ClinicalTrials.gov which periodically has missing or outdated information
- Lack of repetition of the published studies search terms due to limitation of the search structure within the ClinicalTrials.gov database
- Time restraints for complete saturation of interviews

CONCLUSIONS

This review included 23 ongoing interventional studies examining EED-related outcomes. It demonstrates that the majority of ongoing interventional trials for EED are in those intervention types concerned with repair of gut mucosa and epithelial cells, micronutrients and supplemental nutritional therapies. However, the largest planned trials aim to target the pathogenic etiology of EED through administration of antibiotics. The results of these trials will not be available for another 4 to 5 years. Age eligibility ranges varied, with most studies looking at maternal factors or children under 5 years of age, which represents the aim to both prevent and treat EED before longer-term consequences arise during key developmental stages. Many studies aimed to target these children post-lactation. Continued refinement of EED definitions, diagnostics, and target population would support efforts to intervene in this chronic condition.

REFERENCES

1. Guerrant RL, Oria RB, Moore SR, Oria MO, Lima AA. Malnutrition as an enteric infectious disease with long-term effects on child development. Nutr Rev. 2008 Sep;66(9):487-505. PubMed PMID: 18752473. PMCID: PMC2562291. Epub 2008/08/30. eng.
2. Dewey KG, Mayers DR. Early child growth: how do nutrition and infection interact? Matern Child Nutr. 2011 Oct;7 Suppl 3:129-42. PubMed PMID: 21929641. Epub 2011/10/05. eng.
3. Smith LE, Prendergast AJ, Turner PC, Mbuya MN, Mutasa K, Kembo G, et al. The Potential Role of Mycotoxins as a Contributor to Stunting in the SHINE Trial. Clin Infect Dis. 2015 Dec 15;61 Suppl 7:S733-7. PubMed PMID: 26602301. PMCID: PMC4657594. Epub 2015/11/26. eng.
4. Crane RJ, Jones KD, Berkley JA. Environmental enteric dysfunction: an overview. Food Nutr Bull. 2015 Mar;36(1 Suppl):S76-87. PubMed PMID: 25902619. PMCID: PMC4472379. eng.

APPENDIX 1: SEARCH TERMS

Search Terms

(D-xylose OR mannitol OR rhamnose) OR "lactulose paracellular uptake" OR "L:M ratio" OR (α1-anti-trypsin OR alpha*anti-trypsin) OR "alanyl-glutamine" OR "plasma cytokines" or "plasma citrulline" OR calprotectin OR lactoferrin OR "lactose tolerance test" OR myeloperoxidase OR MPO OR "REG 1B" OR neopterin OR "plasma LPS core antibody" OR "LPS binding protein" OR "soluble CD14" OR (kynurenine AND tryptophan) OR "K:T ratio" OR "KT ratio" OR "dual sugar absorption test" OR "serum flagellin IgG" OR "serum flagellin IgA" OR "serum ferritin" OR "serum GLP" OR "serum CRP" OR EndoCab OR "Endogenous endotoxin-core antibody")

→ Biomarkers

AND ("EED" OR "Environmental Enteric Dysfunction" OR "Enteric Dysfunction" OR "Tropical Enteric Dysfunction" OR "Tropical Sprue")

→ EED Specific Terms

APPENDIX 2: WORK ORDER

Research Request Form

Date: 6/11/14

Request Name: Alexis Katsis

Work Order ###, Request ###

This Request scope ("***Scope***") is agreed pursuant to and hereby made a part of Work Order ### (the "***Work Order***"), by and between the Bill & Melinda Gates Foundation (the "***Foundation***") and the University of Washington ("***University***"). Capitalized terms not otherwise defined in this Scope shall have the same meaning as set forth in the Agreement between the parties dated March 31, 2011. The Work Order's terms will control over any conflicting terms in this Scope, unless this Scope expressly states otherwise.

SPECIFIC DESCRIPTION OF BRIEFING/PROJECT, INCLUDING PURPOSE AND AUDIENCE:

Background: Environmental enteric dysfunction (EED) is a condition in which repeated enteropathogen infection leads to chronic gut inflammation and the increase of gut permeability. The result is malabsorption of nutrients and thus slowed linear growth (i.e. stunting). There are also links between EED and decreased cognitive development. Given the morbidity consequences of EED on child growth, the Enteric and Diarrheal Diseases (EDD) and Discovery and Translational Sciences (DT&S) teams at the BMGF are investing in studies to further define EED, to understand the causal pathways of pathology and EED's association with morbidity and to build a case for an intervention. While the BMGF does not currently fund intervention trials for EED, the goal is to start funding interventional trials by 2016. As such, a landscape analysis of what trials have already been done, their study designs, endpoints and results and the trials currently being done would help inform decisions about intervention(s) to move forward with.

Objective: The objective of this research is a landscape analysis of the current and past intervention trials that have outcomes related to EED (gut function biomarkers such as L:M ratio, gut microbiome, growth velocity, stunting, cognitive development, etc.). A summary of the hypothesis/rationale for trial, trial design, inclusion criteria, trial size/power, geography, intervention evaluated, endpoints (primary and secondary), outcomes, and reference(s), for both past and current ongoing trials (in which case outcomes will not be known) is requested. In this project, interventions would be defined not just as small molecule therapeutics but also as

prebiotics, probiotics, functional foods, nutritional interventions and WASH interventions.

The landscaping should be scoped according to the following criteria:

- Study was performed on either pregnant women (preventative treatment) or children no greater than 5 years of age.
- Study is a prospective study investigating a specific intervention (or set of interventions) for EED. Retrospective analyses should be excluded.
- The trial should evaluate endpoints relevant to EED (vs. related conditions such as IBD, IBS, Crohn's disease, etc.)
- Intervention could be either EED preventative or treatment.
- Trials looking specifically and exclusively at sickness (e.g. diarrhea) outcomes, without measuring outcomes relative to EED, should be excluded from the landscape.

Additionally, we would request that the consultant reach out to a few key people, under our direction, to make sure the landscaping report is comprehensive and inclusive, in order to fill in gaps in the landscaping report and potentially capture ongoing or planned studies which are not yet reported. The optimal timing for this activity will be discussed once the landscaping analysis is underway.

The Consultant will communicate with the foundation on a regular basis to provide an update on the landscape analysis and discuss ongoing and future activities, including depth and focus of analysis. In addition, the final format and content of the written report will be finalized through ongoing discussions with foundation staff. Consultant will provide the final report via e-mail to Alexis Katsis (Alexis.Katsis@gatesfoundation.org) by a date agreed upon with the Foundation. The Consultant will also participate in a joint teleconference (or alternatively a face-to-face meeting) with the foundation's EDD team to review and discuss the report.

TIMELINE / DUE DATE:

DELIVERABLE: A landscape analysis of the intervention trials that have been done and are being done with outcomes related to EED. Also an analysis of the endpoints of these trials, as outlined above.

SHARING PERMISSION: yes/no

Do you allow the contents and deliverables developed from this work order to be shared and published to the public? If the contents resulting from this work order are shared, the university team will determine the authorship, as well as, any medium and publications used; including, but not limited to: journals, external websites, and symposiums.

No, initially this will be an internal document only.

APPENDIX 3: LIST OF SUBJECT MATTER EXPERTS

Study Abbreviation/Name	**Expert Name and Affiliation**
WASH Benefits:	Stephen Luby, Stanford University
SHINE:	Jean Humphrey, Johns Hopkins University; Andrew Prendergast, Queen Mary University of London
IMAGINE:	Sean Moore, Cincinnati Children's Hospital Medical Center
Lactobacillus reuteri* in Healthy Children:	Margaret Kosek, Johns Hopkins University
Impact of Legumes vs Corn-soy Flour on EED, Zinc Resistant Starch Project, etc.:	Mark Manary, Washington University in St. Louis
BEED:	Tahmeed Ahmed, ICDDR, Bangladesh
ABCD, Toto Bora:	Judd Walson, University of Washington

Other Subject Matter Experts without Current Interventional Studies for EED	Dick Guerrant, University of Virginia
	Bill Petri, University of Virginia
	Jay Berkley, KEMRI Wellcome Trust

APPENDIX 4: TABLE OF ONGOING TRIALS

1) The Impact of Anthelmintic Treatment on the Incidence of Diarrheal Disease in Vietnamese School Children	
Interventions (by arms)	Experimental: 1) Albendazoale 400mg, single, chewable tablet administered at baseline, 3, 6, 9, and 12 months Control: 1) Placebo, single chewable tablet administered at baseline, 3, 6, 9, and 12 months. Albendazoale 400mg, single, chewable tablet administered at 12 months
Primary Outcome Measures	Measured at t=12 months Incidence of diarrheal disease according to WHO guidelines (weekly active and passive case surveillance)
Secondary Outcome Measures	Measured at t=baseline, 0.5, 3, 6, 6.5, 9, 12 months Prevalence and intensity of soil-transmitted helminth infections by real-time PCR and microscopy Changes in fecal microbiota composition by Illumina sequencing Prevalence and intensity of enteric viruses and bacteria that cause diarrhea assessed by real-time PCR and the Luminex xTAG Measured at t=baseline, 3, 6, 9, and 12 months Gastrointestinal Pathogen Panel (during and two weeks after diarrhea cases) Measured at t=baseline, 6, and 12 months Changes in blood cytokine (Th1, Th2, TH17, and Treg) levels by bead-based immunoassays Antibody isotype response to helminth and diarrheal antigens by ELISA Mean z-scores: HAZ, WAZ, WHZ
Contact Name	Jacqueline Leung
PI	Stephen Baker, Nghia Ho Dang Trung, Pham Ngoc Thach, Andrea Graham
Location: Details	Vietnam: Southern, Go Dau district in Tay Ninh province
Age Groups	Recruitment: 6-15 years
Recruitment	Not yet recruiting
Study Results	No Results Available
Enrollment	700
Study Designs	Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Primary Purpose: Treatment

	Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Last Updated	3-Nov-2015
URL	https://ClinicalTrials.gov/show/NCT02597556
Start Date	1-Feb-2016
Completion Date	1-Aug-2017

2) Combined Package of Interventions for Environmental Enteropathy	
Interventions (by arms)	Experimental: 1) Albendazole (single dose) + Zinc (2 weeks) + MMNs supplement (24 weeks) Control: 1) 3 Placebos
Primary Outcome Measures	Measured at t=12 and 12 weeks Dual Sugar Absorption Test: lactulose mannitol ratio in urine
Secondary Outcome Measures	Measured at t=12 and 12 weeks Lactulose Excretion: percentage of ingested lactulose excreted in urine Mannitol Excretion: percentage of ingested mannitol excreted in urine
Contact Name	No information available
PI	Mark Manary
Location: Details	Malawi: Limela, Machinga District
Age Groups	Eligibility: 12 Months to 35 Months
Recruitment	Completed
Study Results	No Results Available
Enrollment	253
Study Designs	Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Primary Purpose: Treatment Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Last Updated	2-Jun-2015
URL	https://ClinicalTrials.gov/show/NCT02253095
Start Date	1-Oct-2014
Completion Date	1-Apr-2015

3) Water-based Zinc Efficacy Trial in Beninese School Children	
Interventions (by arms)	Experimental: 1) Pump water purified and zinc-fortified by the LifeStraw filtering device (*5 mg of zinc/l of filtered water estimated from device*) Control: 1) Pump water purified by the LifeStraw filtering device 2) No intervention-untreated pump water (pump water recognised as improved water source by WHO)
Primary Outcome Measures	Measured at t=baseline, midpoint (varying between weeks 5-20), 22 weeks Serum zinc concentration
Secondary Outcome Measures	Measured at t=baseline, midpoint (varying between weeks 5-20), 22 weeks Inflammation status: Concentration of CRP in serum Iron status: Haemoglobin level Anthropometric indices: Measurement of height, weight and MUAC for the assessment of HAZ, WAZ and BMI
Contact Name	Michael B Zimmermann
PI	Michael B Zimmermann
Location: Details	Benin: Kotopounga primary school, Natitingou, Atacora
Age Groups	Eligibility: 6-10 years
Recruitment	Completed
Study Results	No Results Available
Enrollment	278
Study Design	Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Last Updated	9-May-2014
URL	https://ClinicalTrials.gov/show/NCT01790321
Start Date	1-Feb-2013
Completion Date	1-Jul-2013

4)	SHINE Sanitation, Hygiene, Infant Nutrition Efficacy Project	Nested case-control study: Maternal Environmental Enteropathy
Interventions (by arms)	Experimental: 1) WASH and Standard Care 2) Nutrition and Standard care - IYCF education - 20 g/d Nutributter from 6-18 months 3) WASH, Nutrition, and Standard Care Control: 1) Standard care - Exclusive Breastfeeding from birth to 6 months - PMTCT services - Strengthen Village Health Worker System	
Primary Outcome Measures	<u>Measured at t=18 months of age</u> Infant recumbent length measured by length board Infant hemoglobin measured by Hemocue	LBW, neonatal mortality, stunting, miscarriage, stillbirth
Secondary Outcome Measures	<u>Measured at t=1, 3, 6, 12 and 18 months of age</u> EED Biomarkers of gut function and structure microbial translocation, systemic inflammation, and hormonal determinants of growth and anemia <u>Measured at t=1-18 months of age</u> Infant diarrhea prevalence, incidence and severity assessed by 7-day morbidity history in all infants, and by daily morbidity diary in a subgroup of infants <u>Measured at t=18 months of age</u> Infant weight, MUAC, and head circumference <u>Measured at t=1, 3, 6 and 12 months of age</u> Infant weight, length, MUAC, and head circumference <u>Measured at t=6 months of age</u> Prevalence of exclusive breastfeeding among all infants enrolled in the trial by	

	maternal/infant HIV status <u>Measured at t=6-18 months of age</u> Diet quality as assessed by WHO IYCF indicators, infant nutrient intake from complementary foods assessed by 24 hour dietary recall, and appropriate use of Nutributter <u>Measured throughout follow-up</u> WASH:Proper disposal of animal and human feces, handwashing with soap after fecal contact, point-of-use chlorination of drinking water, protecting children from ingestion of dirt and feces, feeding baby freshly prepared foods, or reheating leftover food Program Implementation Pathways: Assessment of quality of VHW training and supervision; VHW Capacity, defined as a composite of attained knowledge, goal setting capacity, and achieved performance; Fidelity of intervention implementation, defined as degree of conformance with protocol specifications for both VHW and mother; Attained maternal knowledge and skills assessed by questionnaire and observation; Uptake or adoption of promoted behaviors by mothers and their households assessed by questionnaire and observation.	
Contact Name	n/a	
PI	Jean H Humphrey	
Location: Details	Zimbabwe: Chirumanzu or Shurugwi districts	
Age Groups	Eligibility: Women 15-49 Years Children born into cohort	Eligibility: 12.5 weeks gestational age
Recruitment	Active, not recruiting	Not recruiting
Study Results	No Results Available	Analyses: 1) lab work completed - middle of 2017 2) all data by primary endpoints stunting - Dec-2017 3) secondary objectives - June 2018
Enrollment	5272	Information not available
Study Design	Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Factorial Assignment Primary Purpose: Prevention Masking: Open Label	Nested Case-Control
Last Updated	28-Sep-2015	N/A
URL	https://ClinicalTrials.gov/show/NCT01824940	N/A

Start Date	1-Nov-2012	Information not available
Completion Date	1-Dec-2017	30-Apr-2017

5) WASH Benefits Kenya	
Interventions (by arms)	Experimental: 1) Water quality 2) Sanitation 3) Hand washing 4) Water quality, Sanitation, Hand washing (Combined WASH) 5) Nutrition 6) Nutrition, Water quality, Sanitation, Hand washing Control: 7) No intervention, Active (Village level promoter measure MUAC in children also conducted in experimental arms) 8) No intervention, Passive
Primary Outcome Measures	<u>Measured at t=24 months post intervention</u> LAZ <u>Measured at t=12 and 24 months post intervention</u> Diarrhea Prevalence using caregiver-reported symptoms with 2-day and 7-day recall
Secondary Outcome Measures	<u>Measured at t=12 months post intervention</u> LAZ <u>Measured at t=24 months post intervention</u> Stunting Prevalence using standardized Z-scores ASQ Child Development Scores <u>Measured at t=12 and 24 months post intervention</u> L:M ratio in urine Total IgG antibody titers Myeloperoxidase, alpha 1-antitrypsin, and neopterin levels in stool
Contact Name	Clair Null Tadeo Muriuki
PI	Clair Null Michael Kremer
Location: Details	Kenya: Bungoma and Kakamega
Age Groups	Women who self-identify as pregnant at the time of the baseline and children born into cohort

Recruitment	Recruiting
Study Results	No Results Available
Enrollment	8000
Study Design	Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Primary Purpose: Prevention Masking: Single Blind (Investigator)
Last Updated	29-Aug-2013
URL	https://ClinicalTrials.gov/show/NCT01704105
Start Date	1-Sep-2012
Completion Date	1-Nov-2016

6) WASH Benefits Bangladesh	
Interventions (by arms)	Experimental: 1) Water quality 2) Sanitation 3) Hand washing 4) Water quality, Sanitation, Hand washing (Combined WASH) 5) Nutrition 6) Nutrition, Water quality, Sanitation, Hand washing Control: 7) No intervention
Primary Outcome Measures	<u>Measured at t=24 months post intervention</u> LAZ <u>Measured at t=12 and 24 months post intervention</u> Diarrhea Prevalence using caregiver-reported symptoms with 2-day and 7-day recall
Secondary Outcome Measures	<u>Measured at t=12 months post intervention</u> LAZ <u>Measured at t=24 months post intervention</u> Stunting Prevalence using standardized Z-scores ASQ Child Development Scores <u>Measured at t=12 and 24 months post intervention</u> Lactulose to mannitol ratio in urine measured Total IgG antibody titers
Contact Name	Stephen P Luby
PI	Leanne Unicomb
Location	Bangladesh
Age Groups	Eligible: Women up to 63 years Infants in utero at baseline (target child) <u>Diarrhea measurement</u> Children < 36 months old at baseline that are living in the compound of a target child

	Intestinal parasite specimen collection Children 18 - 27 months living in the compound of a target child
Recruitment	Recruiting
Study Results	No Results Available
Enrollment	5040
Study Designs	Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Primary Purpose: Prevention Masking: Single Blind (Investigator)
Last Updated	26-Jul-2015
URL	https://ClinicalTrials.gov/show/NCT01590095
Start Date	1-May-2012
Completion Date	1-Apr-2016

7) Lao Zinc Study: Effects of Two Forms of Daily Preventive Zinc Versus Therapeutic Zinc Supplementation	
Interventions (by arms)	Experimental: 1) Micronutrient powder (MNP): MNP containing 10 mg Zn + 14 other nutrients, ORS, and placebo tablets for treatment of diarrhea 2) Preventive zinc supplementation: 7 mg dispersible Zn tablets given between meals, ORS, and placebo tablets for diarrhea 3) Therapeutic zinc supplementation: 20 mg dispersible Zn tablets given for 10 days during diarrhea episodes, ORS, and placebo preventive tablets given daily Control: 1) Placebo preventive supplementation: Placebo powder, ORS, and placebo tablets given for 10 days during diarrhea episodes
Primary Outcome Measures	<u>Measured at t=36 weeks</u> Change in length and LAZ Change in weight and WAZ Incidence of diarrhea Change in stool calprotectin & neopterin concentration Change in hair cortisol concentration Intestinal protozoa parasite infection assessed by a modified formalin-ethyl acetate concentration technique Helminth parasite infections will be assessed using duplicate Kato-Katz thick smears <u>Measured at t=32 weeks</u> Change in hemoglobin concentration Change in micronutrient status: plasma zinc, ferritin, transferrin receptor; and retinol binding protein (RBP) concentrations, measured in a subsample of 560 participants, and controlling for the presence of elevated acute phase protein Innate and adaptive immune defense: production of cytokines by cultures of peripheral blood white blood cells; and change in concentrations of naïve and memory CD4 and CD8 T-cells and regulatory (Treg) T-cells in a sub-set of 500 children
Secondary Outcome Measures	<u>Measured at t=36 weeks</u> Change in MUAC <u>Measured at t=4, 8, 12, 16, 20, 24, 32, & 36</u> Achievement of gross motor developmental milestones-World Health Organization include: sitting without support, crawling, standing with assistance, walking with assistance, standing alone, walking alone <u>Measured at t=36 weeks</u>

	Incidence of serious adverse events, including death and required overnight stay in a health facility Incidence of any non-serious adverse events-non-serious adverse events that may be detected retrospectively, such as the incidence of diarrhea, vomiting, etc., based on the results of morbidity surveillance
Contact Name	Sonja Y Hess; Ryan Wessells
PI	Sonja Y Hess
Location: Details	Lao PDR: Four study groups in rural communities in Khammouane Province
Age Groups	Eligibility: 6-23 months
Recruitment	Recruiting
Study Results	No Results Available
Enrollment	3400
Study Design	Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Primary Purpose: Prevention Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Last Updated	2-Dec-2015
URL	https://ClinicalTrials.gov/show/NCT02428647
Start Date	1-Sep-2015
Completion Date	1-May-2017

8) Supplementing Maternal and Infant Diet With High-energy, Micronutrient Fortified Lipid-based Nutrient Supplements (LNS)	
Interventions (by arms)	Experimental: 1) Women during pregnancy: 1 sachet of LNS-P&L (20 g of LNS, for pregnant or lactating women) daily until delivery Women during lactation (from delivery to 6 months post-partum): 1 daily sachet of LNS-P&L (20 g of LNS) Children from 6 to 18 months of age: 2 daily sachet of LNS-20gM (20 g of LNS) Control: 1) Women during pregnancy: 1 tablet of iron+ folate daily until delivery (60 mg iron + 400 ug folic acid) Women during lactation (from delivery to 6 months post-partum): 1 daily tablet of calcium (200 mg) Children from 6 to 18 months of age: None 2) Women during pregnancy: 1 tablet of multiple micronutrients daily until delivery Women during lactation (from delivery to 6 months post-partum): 1 daily tablet of multiple micronutrients' Children from 6 to 18 months of age: None
Primary Outcome Measures	Measured at t=~20 weeks post enrollment (within 48 hours) Birth weight Measured at t= 1 week of age Newborn length Measured at t=18 months of age LAZ
Secondary Outcome Measures	Measured at t=~36 wk gestation and 6 months postpartum Anthropometric status: weight, BMI, MUAC and triceps and sub-scapular skin-fold thickness Anaemia and iron status (Hb, ZPP, transferrin receptor), other micronutrient status (vitamin A, B-vitamins, zinc), malarial antigen Malaria immunity Measured at t=delivery Gestational age, proportion of preterm deliveries Placental malaria histology Measured at t=birth Proportion of low birth weight babies Evidence of defined bacteria in the chorionic membranes at delivery (quantitative DNA amplification method)

	Measured at t=~36 weeks gestation Red blood cell essential fatty acid status, Urinary iodine, Total plasma cholesterol concentration, Blood pressure Measured at t=~28 and ~36 weeks gestation Basal salivary cortisol concentration Measured at t=6 months postpartum Breast milk composition (essential fatty acids, vitamin A, B-vitamins) Maternal cognition Measured with several different tests: Mother - child interaction-Measured with a number of observational tests and questionnaires Measured at t= 4 weeks and 6 months postpartum Depressive symptoms (which may be related to essential fatty acid status) Measured at t=pregnancy Incidence of febrile malaria episodes Measured at t=32 weeks gestation and at delivery Peripheral blood malaria parasitaemia Measured at t=1 week post delivery Prevalence of Neisseria gonorrhoea, Chlamydia trachomatis, in swab samples taken from maternal uterine cervix(qualitative DNA amplification method) Prevalence of bacterial vaginosis, Trichomonas vaginalis, or candidiasis, in swab samples taken from maternal vagina(direct microscopy) Prevalence of maternal periodontitis Measured at t=7 days of age, 6, 12, and 18 months of age Anthropometric infant status: weight, length, head circumference and MUAC Measured at t=6, 12, and 18 months of age Child feeding practices and maternal report of child sleep patterns Basal salivary cortisol concentration Measured at t=6 and 18 months of age

	Infant anaemia and iron status (Hb, ZPP), micronutrient (vitamin A, B-vitamins) and essential fatty acids status, evidence of acute inflammation (CRP, AGP), and malarial antigen and microscopy Cortisol response to acute stress Malaria immunity <u>Measured at t= ≤28 days</u> Incidence of neonatal hospitalizations <u>Measured between t=0 and 18 months of age</u> Clinical morbidity Achievement of five motor milestones and four other developmental milestones <u>Measured at t=18 months of age</u> Antibody response to measles vaccination Neurobehavioral development <u>Measured at t=pregnancy and 18 months of infant age</u> Incidence of serious adverse events <u>Measured at t=1-6, 9, 12, 15, 18, 21, 24, 27, and 30 months of age</u> The composition of intestinal microbiota
Contact Name	Per Ashorn
PI	Per Ashorn
Location: Details	Malawi: rural
Age Groups	Eligibility and follow-up: Mother during pregnancy and six months thereafter and to the child from 6 to 18 months of age
Recruitment	Active, not recruiting
Study Results	No Results Available
Enrollment	1391
Study Design	Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Primary Purpose: Prevention Masking: Single Blind (Outcomes Assessor)
Last Updated	1-May-2015
URL	https://ClinicalTrials.gov/show/NCT01239693
Start Date	1-Feb-2011

Completion Date	1-Dec-2015

9) Complementary Food Supplements for Reducing Childhood Undernutrition	
Interventions (by arms)	Experimental: 1) Wheat Soy Blend (WSB++,) contains added vitamins and minerals - WFP-developed snack given daily 2) Chickpea based complementary food supplement with added milk powder, oil, sugar and added vitamins and minerals given daily 3) Rice based complementary food supplement, with added vitamins and minerals (locally-developed) given daily Control: 1) No food, mothers will receive nutrition education about continued breastfeeding and adequate complementary feeding throughout the period of 6-18 months of age 2) Plumpy Doz - prepackaged, lipid-based Plumpy'Doz (Nutriset, Mulaunay, France), daily
Primary Outcome Measures	<u>Measured at t=6 and 18 months</u> Change in LAZ and WLZ scores <u>Measured at t=18 months</u> Prevalence of stunting and wasting
Secondary Outcome Measures	<u>Measured at t=6-18 months</u> Morbidity (weekly) assessed for a year and episodes of diarrhea, dysentery ALRI, and fever will be recorded <u>Measured at t=6, 9, 12 months</u> Body composition - bioelectrical impedance analysis will be used to look at body composition changes from baseline until 18 months of age <u>Measured at t=at 6, 12, 18 months</u> Maternal knowledge, attitude and practice related to infant and young child feeding <u>Measured at t=At 18 months</u> Cognitive and motor function (Bayley III) Micronutrient status: Iron, vitamin A, zinc and other micronutrient status of children will be examined by intervention group <u>Measured at t=at 24 months</u> Intestinal function - L:M and other biomarkers will be assessed by intervention group and its association with child growth
Contact Name	Parul Christian
PI	Parul Christian

Location: Details	Bangladesh: The JiVitA Project, Johns Hopkins Bangladesh Gaibandha,
Age Groups	Eligibility: 6-8 months
Recruitment	Completed
Study Results	No Results Available
Enrollment	5449
Study Design	Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Primary Purpose: Prevention Masking: Open Label
Last Updated	23-Apr-2015
URL	https://ClinicalTrials.gov/show/NCT01562379
Start Date	1-Sep-2012
Completion Date	1-Nov-2014

10) Zinc Resistant Starch Project	
Interventions (by arms)	Experimental: 1) Resistant starch feeding -- given to mothers and integrated into the food from days 3-35, five weeks Control: 1) Pre-post zinc measures from zinc isotope test at days 1 and 38
Primary Outcome Measures	Measured at t=baseline and 4 weeks Net zinc balance by zinc isotopes quantified in feces and urine Dual Sugar Absorption Test (100 mL): lactulose: mannitol ratio in urine
Secondary Outcome Measures	Measured at t=baseline and 4 weeks Dual Sugar Absorption Test (100 mL): lactulose: mannitol ratio in urine Weight and height changes Measured at t=4 weeks Number of participants with adverse events
Contact Name	Mark Manary
PI	Mark Manary
Location: Details	Malawi: Must live close to Chipalonga Health Center
Age Groups	Eligibility: 36-60 months
Recruitment	Recruiting
Study Results	No Results Available
Enrollment	20
Study Design	Endpoint Classification: Safety/Efficacy Study Intervention Model: Single Group Assignment Primary Purpose: Treatment Masking: Open Label
Last Updated	12-Mar-2013
URL	https://ClinicalTrials.gov/show/NCT01811836
Start Date	1-Mar-2013
Completion Date	1-Mar-2014

11) Improving the Nutrition Status of Infants in South-Western Uganda	
Interventions (by arms)	Experimental: 1) Nutritional education for mothers Control: 1) No intervention
Primary Outcome Measures	Measured between t= 6-8, 12-14, 18-20, 36 months Change in the prevalence of stunting (<-2 SD of the WHO, 2006 growth reference standards) Measured between t= 12-14, 18-20, 36 months Change in the Bayley Mental Development Index
Secondary Outcome Measures	Measured between t=6-8, 12-14, 18-20, 36 months Change in mean WAZ Change in mean weight for HAZ Change in mean MUAC Change in mean diet diversification score (DDS) Change in Ages and Stages Questionnaire Scores (ASS) Change in Bayley Child Development test 3 ed. Measured between t=12-14, 18-20, 36 months Change in gut microbiota: fecal samples Measured at t=36 months Change in Kaufman Assessment Battery for Children (KABC)
Contact Name	Per Ole Iversen
PI	Per Ole Iversen
Location: Details	Uganda: Kampala, Kyambogo University
Age Groups	Eligibility: 6-36 months
Recruitment	Active, not recruiting
Study Results	No Results Available
Enrollment	510
Study Design	Allocation: Randomized|Intervention Model: Parallel Assignment|Primary Purpose: Prevention|Masking: Open Label
Last Updated	1-Dec-2015
URL	https://ClinicalTrials.gov/show/NCT02098031
Start Date	1-Mar-2014
Completion Date	1-Jul-2016

12) Safety of Lactobacillus Reuteri in Healthy Children Aged 2-24 Months	
Interventions (by arms)	Experimental: 1) 1 x 10e8 CFU *Lactobacillus reuteri* 17938 suspended in sunflower oil, medium chain triglyceride oil, silicone dioxide. 1 drop administered daily for 5 days Control: 1) Sunflower oil, medium chain triglyceride oil, silicone dioxide suspension. 1 drop administered daily for 5 days
Primary Outcome Measures	Measured at t=5 and 28 days Monitoring of baseline laboratory tests at following the initiation of therapy and by AE monitoring. Measured at t=28 days Analysis of 28 day diary cards that are distributed to all randomized subjects on which parents record their child's symptoms (specifically fever, anorexia/oral intake, vomiting, diarrhea, irritability, rash, wheezing, or open fields which allows them to describe any issue their child may experience and grade its severity). Number of participants with positive blood culture for L. reuteri Mean daily temperature
Secondary Outcome Measures	Measured at t=3,5,12,15,18,24,28, 36 days Duration of shedding of Lactobacillus reuteri (Lr) strain DSM 17938 following administration determined by an endpoint PCR assay for L. reuteri done on stool
Contact Name	Margaret N Kosek Pablo Yori
PI	Richard A Oberhelman
Location: Details	Peru: rural; clinical trial center
Age Groups	Eligibility: 2-24 months
Recruitment	Not yet recruiting
Study Results	No Results Available
Enrollment	60
Study Designs	Allocation: Randomized Endpoint Classification: Safety Study Intervention Model: Parallel Assignment Primary Purpose: Treatment Masking: Double-Blind
Last Updated	1-Jun-2015
URL	https://ClinicalTrials.gov/show/NCT02460575

Start Date	1-Oct-2015
Completion Date	1-Mar-2016

13) Safety of Lactobacillus Reuteri in Healthy Children Ages 2 to 5 Years in Peru	
Interventions (by arms)	Experimental: 1) 1 x 10e8 CFU *Lactobacillus reuteri* 17938 suspended in sunflower oil, medium chain triglyceride oil, silicone dioxide. 1 drop administered daily for 5 days Control: 1) Sunflower oil, medium chain triglyceride oil, silicone dioxide suspension. 1 drop administered daily for 5 days Nested study: 1) first 30 subjects randomized, administration of each dose of the study preparation drops (A or B above) will be immediately followed by offering 2 ounces of flavored PediaSure ® to assess the impact of concurrent administration of a buffering non-lactose containing formula with prebiotic nutritional properties on intestinal colonization with L. reuteri by PCR
Primary Outcome Measures	Measured at ~t=36 days Number of participants with positive blood culture for L reuteri Measured at t=1,2,3,4 & 5 days Mean daily temperature
Secondary Outcome Measures	Not provided
Contact Name	Margaret N Kosek Pablo Yori
PI	Richard A Oberhelman
Location: Details	Peru
Age Groups	Eligibility: ages 2-5 years
Recruitment	Not yet recruiting
Study Results	No Results Available
Enrollment	60

Study Designs	Allocation: Randomized Endpoint Classification: Safety Study Intervention Model: Parallel Assignment Primary Purpose: Treatment Masking: Double-Blind
Last Updated	20-Nov-2014
URL	https://clinicaltrials.gov/show/NCT02124122
Start Date	1-Feb-2015
Completion Date	June 2015

14) Novel Diagnostics and Probiotics to Improve Management of Paediatric Acute Gastroenteritis	
Interventions (by arms)	Experimental: 1) Rapid diagnostic and antimicrobials for treatable pathogens along with probiotic Lactobacillus reuteri, 5 drops/day (1 x 10e8 CFU) x 2 months 2) Delayed diagnostic, batch testing at conclusion of study period, along with probiotic (not listed but inferred probiotic at enrollment) Lactobacillus reuteri, 5 drops/day (1 x 10e8 CFU) x 2 months Control: 1) Rapid diagnostic and antimicrobials for treatable pathogens with placebo 2) Delayed diagnostic, with placebo
Primary Outcome Measures	Measured at t=60 days post intervention: Mortality
Secondary Outcome Measures	Measured at t=60 days post intervention: HAZ adjusted for initial HAZ "environmental enteropathy score" WAZ adjusted for initial WAZ Measured at t=approximately 4 day intervals Presence and duration of diarrhoea verified with the caregiver by telephone 7 days after the participant was discharged home
Contact Name	Jeffrey Pernica
PI	Jeffrey Pernica
Location: Details	Botswana: Gaborone, Princess Marina Hospital
Age Groups	Eligibility: 3-60 months
Recruitment	Completed
Study Results	No Results Available
Enrollment	76
Study Designs	Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Factorial Assignment Primary Purpose: Treatment Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Last Updated	4-Mar-2015
URL	https://ClinicalTrials.gov/show/NCT02025452
Start Date	1-Mar-2014
Completion Date	1-Dec-2014

15) The Impact of Legumes vs Corn-soy Flour on Environmental Enteric Dysfunction in Rural Malawian Children 1-3 Year Olds	
Interventions (by arms)	Comprising 15% of total daily calorie intake Experimental: 1) Cowpeas complementary food given for 12 months 2) Common bean complementary food given for 12 months Control: 3) Corn-soy flour given for 12 months
Primary Outcome Measures	Measured at t=3, 6, and 12 months Dual Sugar Absorption Test: lactulose mannitol ratio in urine
Secondary Outcome Measures	Measured at t= 3, 6, and 12 months Lactulose Excretion:percentage of ingested lactulose excreted in urine Mannitol Excretion:percentage of ingested mannitol excreted in urine
Contact Name	Indi Tehran
PI	Mark Manary
Location: Details	Malawi: Limela, Machinga District and N tenda (Chikwawa District)
Age Groups	Eligibility: 12 Months to 35 Months
Recruitment	Not yet recruiting
Study Results	No Results Available
Enrollment	300
Study Design	Allocation: Randomized Intervention Model: Parallel Assignment Primary Purpose: Treatment Masking: Single Blind (Investigator)
Last Updated	15-Jun-2015
URL	https://ClinicalTrials.gov/show/NCT02472301
Start Date	1-Aug-2015
Completion Date	1-Aug-2017

16) The Impact of Legumes vs Corn-soy Flour on Environmental Enteric Dysfunction in Rural Malawian Children 6-11 Months	
Interventions (by arms)	Administering 200 kcal/day for children 6-9 months and 300 kcal/day for children 9-11 months Experimental: 1) Cowpeas complementary food given for 6 months 2) Common bean complementary food given for 6 months Control: 1) Corn-soy flour given for 6 months
Primary Outcome Measures	Measured at t=3 and 6 months Dual Sugar Absorption Test: lactulose mannitol ratio in urine
Secondary Outcome Measures	Measured at t=3 and 6 months Lactulose Excretion:percentage of ingested lactulose excreted in urine Mannitol Excretion:percentage of ingested mannitol excreted in urine
Contact Name	Indi Tehran
PI	Mark Manary
Location: Details	Malawi: Limela, Machinga District and Ntenda (Chikwawa District)
Age Groups	Eligibility: 6-12 Months
Recruitment	Not yet recruiting
Study Results	No Results Available
Enrollment	300
Study Design	Allocation: Randomized Intervention Model: Parallel Assignment Primary Purpose: Treatment Masking: Single Blind (Investigator)
Last Updated	15-Jun-2015
URL	https://ClinicalTrials.gov/show/NCT02472262
Start Date	1-Aug-2015
Completion Date	1-Aug-2017

17) Intervention and Mechanisms of Alanyl-Glutamine for Inflammation, Nutrition, and Enteropathy (IMAGINE)	
Interventions (by arms)	Experimental: 1) Alanyl-Glutamine orally 3g/day for 10 days 2) Alanyl-Glutamine orally 6g/day for 10 days 3) Alanyl-Glutamine orally 12g/d for 10 days Control: 1) Glycine orally 12.5 g/d for 10 days
Primary Outcome Measures	Measured at t=1, 10-13, 30-37 days Dual Sugar Absorption Test: lactulose mannitol ratio in urine
Secondary Outcome Measures	Measured at t=1, 10-13 days Fecal Cytokine Measured at t=1, 10-13, 30-37 days Fecal Lactoferrin Fecal Calorimetry Metabolomic Profile of Urine Measured at t=1, 10-13, 30-37, 90-104, 120-141 days HAZ WAZ WHZ Measured at t=1, 30-37, 90-104, 120-141 days History of Diarrhea in the Previous Two Weeks
Contact Name	Sean Moore
PI	Aldo Lima
Location	Brazil
Age Groups	Eligibility: 2 months to 5 years old
Recruitment	Recruiting
Study Results	No Results Available
Enrollment	140
Study Design	Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Primary Purpose: Treatment Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Last Updated	26-Nov-2013

URL	https://ClinicalTrials.gov/show/NCT01832636
Start Date	1-Oct-2013
Completion Date	1-Feb-2016

18) ω3 LCPUFAs for Healthy Growth and Development of Infants and Young Children in Southwest Ethiopia	
Interventions (by arms)	Experimental: 1) Dietary Supplement: Fish powder corn-soy blend + Fish oil capsule Omega 3 food supplement: 500 mg DHA + EPA, daily for 12 months 2) Dietary Supplement: Fish powder corn-soy blend + corn oil capsule Omega 3 capsule: 500 mg DHA + EPA, daily for 12 months 3) Dietary Supplement: Corn-soy blend + fish oil capsule Control (food or capsule): 0 mg DHA + EPA, daily for 12 months Control: 1) Dietary Supplement: Corn-soy blend + corn oil capsule. Control food supplement: 0 mg DHA + EPA, daily for 12 months. Control capsule: 0 mg DHA + EPA, daily for 12 months.
Primary Outcome Measures	<u>Measured at t=baseline-12 months</u> Δ LAZ <u>Measured at t=6 and 12 months</u> Development score using Denver II test and Ages-Stages Social-Emotional Questionnaire
Secondary Outcome Measures	<u>Measured at t=baseline-12 months</u> Head circumference (monthly) MUAC (monthly) C-reactive protein concentration (monthly Haemoglobin concentration (monthly) <u>Measured at t=6 and 12 months</u> WAZ up to 12 months Prevalence of stunting HAZ <-2 Prevalence of wasting (WHZ <-2) Breast milk concentrations of DHA/EPA/AA (6-monthly) Infant blood concentrations of DHA/EPA/AA (6-monthly) <u>Measured at t=1-52 weeks</u> Infant morbidity at weekly intervals (weekly) Infant morbidity (acute respiratory infection, diarrhoea, fever, malaria): weekly recall by caregiver, malaria by microscopy.
Contact Name	None named
PI	Patrick Kolsteren

Location: Details	Ethiopia: Jimma University Jimma
Age Groups	Eligibility: 6-12 months
Recruitment	Active, not recruiting
Study Results	No Results Available
Enrollment	320
Study Designs	Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Primary Purpose: Prevention Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Last Updated	23-Mar-2015
URL	https://ClinicalTrials.gov/show/NCT01817634
Start Date	1-Nov-2013
Completion Date	1-Sep-2015

19) Bangladesh Environmental Enteric Dysfunction (BEED)	
Interventions (by arms)	Experimental: 1) Top-up: 150 mL milk and 1 egg a day for 2-3months = 180kCal - 2 months for those children at-risk for stunting - 3 months for those children already stunted and malnourished adults
Primary Outcome Measures	Measured at t=0 and 2 or 3 months (following intervention) Change in anthropometric measures (LAZ mentioned)
Secondary Outcome Measures	Measured at t=0 and 2 or 3 months (following intervention) Levels of biomarkers: Alpha1 anti-tripsan, neopterin, Reg1B, calprotectin, L:M ratio, tryptophan kineranine ratio, soluble CD-14, serum ferritin, CRP-agp (and a couple of others…) Measured at t=2 or 3 months histopathology - Endoscopy in those who do not respond to the top-up, projected about 20% of the sample
Contact Name	N/A
PI	Tahmeed Ahmed
Location	Bangladesh
Age Groups	Eligibility: children - 12-18 months; adults - 18-45 years
Recruitment	Planned
Study Results	N/A
Enrollment	1,500 of 6,000 randomized to nutritional treatment (500 stunted, 500 at-risk, and 500 adults); anticipate biopsies on 100 subjects
Study Designs	Nested cohort, endoscopy in poor responders; community identified
Last Updated	N/A
URL	N/A
Start Date	Apr-16
Completion Date	Dec-19

20) Randomized, double blind, placebo controlled trial comparing the impact of lactoferrin and lysozyme supplementation versus placebo in the treatment of sub-clinical environmental enteropathy in rural Malawian children	
Interventions (by arms)	Experimental: 1) 1.5g/day of bovine lactoferrin combined with 0.2g/day recombinant human lysozyme: single daily sachet of rice powder added to be added to maize porridge Control: 1) Placebo: milled rice powder to be added to maize porridge
Primary Outcome Measures	Measured at t=1, 56, and 112 days Δ urinary lactulose:mannitol ratio (L:M)
Secondary Outcome Measures	Adverse gastrointestinal symptoms Measured at t=1, 28, 56, 84, 112 days Anthropometric measure changes (measured by MUAC and height boards) Measured at t=1, 56, and 112 days Amounts of lactulose and mannitol excreted in the urine as a percentage of the amount ingested before and after the intervention Changes in the stool microbiome through mRNA expression of S100A8, BIRC3, CDX1, FAM65B, HLA-DRA, LCN2, LCT, SI and REG1B.
Contact Name	None named
PI	Mark Manary, Ken Moleta?
Location: Details	Malawi: Machinga District
Age Groups	Eligibility: 12-24 months
Recruitment	Information not available
Study Results	N/A
Enrollment	250
Study Designs	Randomized, double blind, placebo controlled trial
Last Updated	N/A
URL	N/A
Start Date	Information not available
Completion Date	12/31/16

21) Automatic Chlorination and Child Health in Urban Bangladesh	
Interventions (by arms)	Experimental: 1) Water chlorination: Flogenic - The chlorine doser delivers a constant amount of chlorine into water as it flows into a holding tank. The water is then piped to public and private taps. Control: 1) Vitamin C dosing into water. Primary drinking water source will be outfitted with automatic dosing device supplied with vitamin C tablets.
Primary Outcome Measures	Measured at t=0, every 2-3 months for 16 months Diarrhea longitudinal prevalence *1-week recall period, case definition is 3 or more loose/watery bowel movements in 24 hours*
Secondary Outcome Measures	Measured at t=0, every 2-3 months for 16 months WAZ, respiratory illness longitudinal prevalence (*one week recall period, symptoms include congestion, cough, difficulty breathing*), severe diarrhea (*prevalence of diarrhea cases requiring hospitalization*), caregiver defined diarrhea (*1-week recall period, defined with local Bengali word for diarrhea*) Measured at t=0 and 16 months (study conclusion) HAZ, C-reactive protein, total IgG Measured 6-12 months after intervention delivery Prevalence and number of enteric pathogens
Contact Name	Amy Pickering; Steve Luby
PI	Stephen Luby
Location	Bangladesh: Dhaka
Age Groups	Eligibility: Households with at least one child under 60 months old; Households using enrolled shared water point as primary drinking water source
Recruitment	Recruiting
Study Results	N/A
Enrollment	2000
Study Designs	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor) Primary Purpose: Prevention
Last Updated	17-Mar-16

URL	https://clinicaltrials.gov/ct2/show/NCT02606981
Start Date	Jul-15
Completion Date	December 2016 (final data collection date for primary outcome measure)

22) Toto Bora: Azithromycin (AZM) to prevent post-discharge morbidity and mortality in Kenyan children	
Interventions (by arms)	Provided at hospital discharge Experimental: 1) 5-day course of azithromycin (10 mg/kg on day 1, followed by 5mg/kg/day on days 2-5) Control: 1) 5-day course of placebo
Primary Outcome Measures	Measured at t=baseline, 90 days & 6 months Mortality or hospital re-admission
Secondary Outcome Measures	Measure at t=90 days & 6 months Anthropometric measurements: height/length, weight, MUAC Collected at t=baseline, 90 days & 6 months (n=1400) Stool: Parasite testing and antimicrobial susceptibility testing (AST), one or more of the following: enteric infection detection and quantification using multiplex real-time PCR methods, DNA extracted for metagenomic analysis to determine the composition of the microbial communities. Blood: Pro-inflammatory cytokine Nasopharyngeal swabs: Pneumococcal colonies Collected at t=baseline, 90 days & 6 months (n=300) Stool: commercially available enzyme-linked immunosorbent assays: neopterin (NEO), alpha-anti-trypsin (AAT), myeloperoxidase (MPO)
Contact Name	Judd Walson
PI	Judd Walson, Benson Singa
Location: Details	Kenya: Western Kenya
Age Groups	Eligibility: 1-59 months admitted to hospital for non-trauma conditions and subsequently discharged
Recruitment	Planned, 4/1/2016
Study Results	N/A
Enrollment	1400 (300 in nested cohort)
Study Designs	Randomized, double-blind, placebo-controlled clinical trial with nested randomized cohort called the Enteric Function Cohort
Last Updated	N/A
URL	N/A
Start Date	planned: 04/01/16
Completion Date	estimated: 02/29/20

23) ABCD trial	
Interventions (by arms)	Experimental: 1) 3-day course of azithromycin: 1 dose per day, 10mg/kg in morning 2) 3-day course of ciprofloxacin: 2 doses per day, 15 mg/kg in the morning and evening Control: 1) Same dosing containers and schedule - "will be similar in all aspects including the content, color and taste."
Primary Outcome Measures	Measured at t=0 and 90 days Δ LAZ Measured at t=90 days All-cause mortality
Secondary Outcome Measures	Measured at t=90 days Δ MUAC and Δ WHZ, cause-specific mortality (*verbal autopsy*), risk of mortality associated with the presence of antimicrobial resistance genes in stool conferring macrolide, β-lactamase and quinolone resistance Measured at t=0 days proportion of strains of E. coli, isolated from stools, and S. pneumococcus, isolated from nasopharyngeal swab, resistant to macrolide, β-lactamase and quinolone antibiotics Measured at t=0, 90, 180 days (subset of 25%) proportion of strains of E. coli, isolated from stools, and S. pneumococcus, isolated from nasopharyngeal swab, resistant to macrolide, β-lactamase and quinolone antibiotics
Contact Name	Information unavailable
PI	Information unavailable
Location: Details	Bangladesh, India, Pakistan, Kenya, Malawi, Mali, and Tanzania: 2-10 sites per country
Age Groups	Eligibility: 2-23 months, presenting to health facility with diarrhea, without blood in stool
Recruitment	Planned, 1/1/2017
Study Results	N/A
Enrollment	15,000 (Stool sample or rectal swab in 25% of enrolled - will have an additional follow-up at 180 days)
Study Designs	Randomized, multi-country, multi-site, double-blind, placebo-controlled clinical trial
Last Updated	N/A
URL	N/A
Start Date	N/A
Completion Date	~August 2020