Microbial Interventions - Target Product Profile

Disease Area: Maternal, Newborn and Child Health
Intervention: Microbial Interventions (Probiotics and Live Biotherapeutic Products) during pregnancy and lactation to promote maternal health

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This is a draft document and is undergoing public consultation. It is anticipated that the contents and structure of this document may change during this process.

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1 Background

1.1 Maternal Gut Microbiome and Undernutrition

The gut microbiome has been identified as an important, yet not entirely understood, factor influencing maternal, fetal and infant health outcomes.[1,2] The human gut microbiome (made up of predominantly bacteria, but also viruses, archaea and eukaryotic microbes[3]) influences many physiological functions including metabolic functions, immune system regulation, prevention of infection, and inflammatory responses.[4] An altered gut microbiome in a state of dysbiosis – defined as an "unhealthy imbalance in microbial composition"[5] – has been shown to play a role in multiple diseases and conditions, such as gastrointestinal disorders, colorectal cancer, diabetes, mental health conditions and cardiovascular disease.[6,7] Pregnancy-induced changes to the gut microbiome, including reduced microbial diversity, are believed to be in part due to normal hormonal and weight changes during pregnancy.[5] In addition, gut dysbiosis can impact, and be influenced by, nutritional status during pregnancy.[8,9]

Microbial dysbiosis is hypothesized to be associated with adverse pregnancy outcomes including preterm birth, gestational diabetes, hypertension, and early-onset preeclampsia.[10,11] Preliminary evidence from studies involving fecal microbiota transplants from women diagnosed with preeclampsia into mice models have demonstrated a manifestation of preeclampsia-related symptoms including elevated blood pressure both prior to conception and during pregnancy, as well as increased concentrations of urine proteins.[12,13] Furthermore, a study employing fecal microbiota transplant on pregnant mice from women with gestational diabetes demonstrated increases in blood glucose levels.[14]

One proposed mechanism by which microbial dysbiosis may influence maternal outcomes is through altering the ability of the gut to absorb nutrients. Maternal undernutrition is highly prevalent in many low- and middle-income countries (LMICs), particularly African and South Asian countries.[15] Global estimates highlight undernutrition as a key contributing factor in 3.5 million deaths of mothers and children under five annually.[16] The etiology of maternal undernutrition is complex, with a multitude of factors contributing to its development, including insufficient food intake, poor dietary diversity and a decreased ability to absorb and efficiently process nutrients.[17] For example, microbiome-related conditions, as well as some infectious diseases, and inflammatory conditions (e.g. irritable bowel syndrome) can impair the

body's ability to absorb nutrients.[18,19] As a result, even if a woman consumes sufficient nutritious food, they may still be undernourished.

Though the relationship between gut microbiome and adverse pregnancy outcomes is complex, it is hypothesized that undernourished pregnant women are more likely to develop environmental enteric dysfunction (EED), and vice versa.[20] EED is characterized by subclinical inflammation in the small intestine, causing poor macro/micronutrient absorption capacity, altered gut morphology and impaired barrier function.[20] There is limited evidence on the prevalence of EED specifically in pregnant women, however it is believed to be particularly common across non-pregnant populations in low- and middle-income countries.[21] For example, a growing body of evidence has demonstrated the high prevalence of EED in young children in LMICs.[10] Thus, therapeutics that can prevent or treat gut dysbiosis may have beneficial effects on maternal and newborn outcomes.

1.2 Current Products

There are several different types of microbial interventions aimed at optimizing gut microbiome, with varying mechanisms of action, modes of administration, and evidence of efficacy and acceptability. Some interventions take a targeted approach aiming to influence (either increase or decrease) specific microbial strains or taxa, whereas other interventions act more broadly, aiming to affect the entire 'community' of gut microbiota.[22]

Many of these interventions aim to improve maternal gut and systemic inflammation, gut permeability, pathogen burden and microbiome composition which may be linked to poor maternal and infant outcomes. Some microbial therapeutics may also have the potential to augment (or be adjunct to) other therapies, such as co-administration with antibiotics to reduce the risks of anti-microbial resistance and decreased gut microbiome diversity.[23,24] Microbiome-altering interventions/products may thus have the potential to enhance health outcomes for undernourished women and their babies.

This TPP focuses on two types of microbial interventions – probiotics and live biotherapeutic products (LBP):

- Probiotics – defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host".[25] There are many types of probiotics, and these can be either foods or supplements. Commonly used

bacterial genera in probiotics include *Lactobacillus, Bifidobacterium, Escherichia, Enterococcus, Bacillus* and *Streptococcus*.[26]

- Live Biotherapeutic Products (LBPs) – the FDA defines LBPs as biological products that "1) contains live organisms, such as bacteria; 2) is applicable to the prevention, treatment, or cure of a disease or condition of human beings; and 3) is not a vaccine"[27] LBPs can consist of either a single or multiple microbial strains, and their functionalities may arise from genetic engineering or through innate processes of the microbes.[28]

There are other more specialized interventions that target gut microbiome - including faecal microbiota transplant and phage therapy[22] – that are beyond the scope of this TPP.

Although related, there are differences between probiotics and LBPs. A key distinction lies in their intended purpose: probiotics aim to provide general health benefits, whereas LBPs are intended to treat specific conditions or diseases.[29] The differing intended purposes of these products results in differences regarding regulatory requirements. LBPs are regulated as drugs, while probiotics supplements face less stringent regulatory measures. There are LBPs currently on the market indicated for skin conditions (e.g. atopic dermatitis, acne vulgaris, chronic wounds[30]) and gastrointestinal disorders (e.g. irritable bowel syndrome[31,32]). However, there are currently no commercially available LBPs specifically for maternal health conditions.

1.3 Purpose of this Target Product Profile on Microbial Interventions

Target Product Profiles (TPPs) are strategic documents that outline the minimum and optimal characteristics required for new health products, including medicines and devices. TPPs are an important resource to guide key stakeholders (such as funders, researchers, product developers, manufacturers and regulators) on the requirements of new medicines, diagnostics and devices to meet pre-specified clinical and public health needs.[27] They inform research and development strategies, help frame product dossiers, streamline communication with regulatory agencies and help funders set targets.[33]

Interventions that target maternal microbiome composition have the potential to correct gut dysbiosis, which has been associated with maternal undernutrition, and other complications of pregnancy.[9,34] The use of microbiome-altering interventions to correct gut dysbiosis in pregnancy and postpartum is an emerging area of research.[11,22]

If targeting the maternal gut microbiome and alleviating EED was shown to be safe and effective in improving maternal and infant health outcomes, it could help prevent the adverse consequences of maternal gut dysbiosis.

There are currently no TPPs publicly available for microbiome-altering interventions in maternal health. Development of this TPP is intended to help drive innovation, research and implementation of effective interventions that can alter the maternal enteric microbiome, to improve outcomes of mothers and babies globally.

2 Summary: Intervention Use and Target Users

A therapeutic supplement (probiotics) or drug (LBPs) that targets the maternal gut microbiome in pre-conception, pregnant and lactating women. The product should impact maternal gut and systemic inflammation, gut permeability, pathogen burden and microbiome composition and function that are linked to both maternal (e.g. gestational diabetes, hypertension, obesity, preeclampsia, maternal infection) and infant (e.g. small for gestational age, preterm birth, low birth weight, sepsis, NEC) outcomes. Interventions should be affordable, and self-administered non-invasively.

The health worker cadre responsible for recommending the intervention may depend on the specific product and country, but could include obstetricians, nurses, midwives, nutritionists or dietitians. Probiotics can be taken orally by an individual woman, without the need for a trained healthcare professional to prepare and administer the product. Live biotherapeutic products are also taken orally by an individual woman, however they typically require a trained health professional to diagnose the condition to be treated and to prescribe the appropriate LBP for that condition.

To ensure the correct target user group has widespread access to any effective microbial interventions, targeted distribution through established healthcare systems would be needed. The interventions should be incorporated into settings or facilities where routine antenatal care and nutrition programs are provided, particularly in settings where gut dysbiosis, EED and maternal undernutrition are prevalent.

3 Executive Summary: TPP Core Variables

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point.*	Optimistic *The optimistic target should reflect what is needed to achieve broader, deeper, quicker global health impact.*	Annotations / Actual Product Performance *For all parameters, include here the rationale for why this feature is important and/or for the target value.*
Indication	Probiotics: Supplement specifically treating women with suspected or confirmed EED and/or symptoms indicative of gut dysbiosis. Live biotherapeutic products: Therapeutic specifically treating women with suspected or confirmed EED and/or symptoms indicative of gut dysbiosis.	Probiotics: Supplement specifically treating undernourished women and/or women with suspected or confirmed EED and/or symptoms indicative of gut dysbiosis. Live biotherapeutic products: Therapeutic specifically treating undernourished women and/or women with suspected or confirmed EED and/or symptoms indicative of gut dysbiosis.	At a minimum, probiotics and live biotherapeutic products are intended to target specific microbiome-related conditions or diseases, such as EED which may contribute to, or mediate, certain pregnancy-related complications.[2,29,35] Additionally, both products optimally would also be able to treat a wider population group of women experiencing undernutrition. Both product types are intended to contribute to improved maternal and fetal outcomes.
Target Population	Pregnant women, lactating women, or women/adolescents of reproductive age preparing for conception, with suspected or diagnosed EED or gut dysbiosis.	Pregnant women, lactating women, or women/adolescents of reproductive age in preparation for conception, who are undernourished, or have suspected or diagnosed EED or gut dysbiosis.	Gut dysbiosis, EED and undernutrition may affect women prior to, during or after pregnancy. Gut dysbiosis can be determined by laboratory diagnostic tests such as

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			stool testing or organic acid (urine) testing.[36,37] EED has traditionally been diagnosed through invasive tests such as endoscopy and small intestinal biopsy.[38] Biomarker tests (e.g. dual-sugar absorption tests) are emerging as alternative diagnostic options.[39] Despite having less resource-intensive requirements in comparison to invasive tests,[40] biomarker tests may also have limited availability in LMICs.[41] Undernourishment is determined by anthropometric measures including low Mid-Upper Arm Circumference (MUAC) and low Body Mass Index (BMI).[42,43]
Special populations	Must be safe and effective for use in undernourished, stunted or wasted women and adolescents, including those in whom nutritional intake is currently limited.	Same as minimum	Products must be safe and effective for use in all women who have any degree of severity of undernutrition.[44] Women taking these products may not have a

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	Safe for women with common conditions of pregnancy such as gestational diabetes and hypertension. Also safe for women with comorbidities such as HIV.		sufficient macro and/or micronutrient intake. Must be safe for use in women with pregnancy-related conditions commonly linked with undernutrition, including preeclampsia[45] and gestational diabetes.[46] Additionally, must be safe for use in HIV-positive women given the significant overlap between HIV and undernutrition, particularly in LMICs.[47]
Population unlikely to be treated	Not intended for women with a medical contraindication to the intervention.	Same as minimum	Women who have a specific contraindication to probiotics or live biotherapeutic products would not be suitable to receive the intervention.
Target Countries	All low-, middle- and high-income countries.	Same as minimum	While applicable to women globally, the burden of maternal undernutrition is more prevalent in low- and middle-income countries (LMICs).[15] While data is limited, gut dysbiosis is also believed to be prevalent in LMICs, in part due to the

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			close linkages between undernutrition and the gut microbiome.[48]
Efficacy	Pre-conception: Reduced gut inflammatory markers. Pregnant women: Reduced gut inflammatory markers. Lactating women: Reduced gut inflammatory markers.	Pre-conception: Reduced gut inflammatory markers. Increase in Body Mass Index (BMI)/Mid-Upper Arm Circumference (MUAC). Pregnant women: Reduced gut inflammatory markers. Improved gestational weight gain. Reduced low birth weight/preterm birth. Lactating women: Reduced gut inflammatory markers. Increase in BMI/MUAC.	Measuring reductions in gut inflammatory markers requires tests (e.g. biopsy, stool, organic acid (urine)) that may not be readily available or of a high quality in low- and middle-income countries.[49,50] Minimum efficacy outcomes reflect the reduction in gut dysbiosis symptoms, namely gut inflammation, indicative of improved gut microbiome composition. Optimistic efficacy outcomes also include increase in weight gain and reduced low birth weight and preterm birth indicative of improved nutritional status in undernourished women.[51]
Safety	Clinical safety (adverse or serious adverse effects for mother and baby) comparable to current therapies.	Fewer adverse effects than current therapies.	Probiotics use during pregnancy and lactation has thus far not found any safety concerns.[52,53]

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	Not contraindicated in pregnant and lactating women. Absence of fetal and embryonic toxicity. Manufacture of product with consistent quality that meets the minimum standards for Codex and national registration requirements, in particular label accuracy.	No drug-related serious adverse events for mother or baby. Not contraindicated in pregnant and lactating women. Absence of fetal and embryonic toxicity. Evidence shows no long-term adverse effects for mothers or babies.	Evidence on the use of live biotherapeutic products during pregnancy and lactation is currently limited. Establishing the safety profile of LBPs for these populations must consider the influence of diverse microbial strains in LBPs as well as potential interactions with the host microbiome.[54]
Need for clinical monitoring	Standard continued monitoring of maternal and fetal health and wellbeing, as per usual antenatal care practices. Minimal additional monitoring required for expected product side-effects.	Standard continued monitoring of maternal and fetal health and wellbeing, as per usual antenatal care practices. In addition, standard monitoring and management for undernutrition. No additional monitoring required for expected product side-effects.	Regular assessment of maternal and fetal wellbeing and growth is recommended during pregnancy.[55] Management of undernutrition can include a range of individually tailored measures to address nutritional deficiencies and underlying causes of inadequate nutrient intake or absorption, such as nutritional assessments, modifications to diets, nutritional supplementation and medical treatments for underlying conditions.[56]

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Is companion diagnostic needed for use?	Additional diagnostic needed to confirm EED and/or gut dysbiosis to ensure appropriate target population is being treated.	Additional diagnostic needed to confirm EED and/or gut dysbiosis to ensure appropriate target population is being treated. Optimally, a diagnostic test for gut dysbiosis or EED that is affordable, accessible, non-invasive and simple to use would be beneficial to implementation in LMICs. For undernourished women, no additional diagnostic is needed beyond standard diagnosis of undernutrition.	Targeting the intervention to a specific population with EED and/or gut dysbiosis may increase effectiveness and efficiency of treatments. In contrast, population level interventions that do not require diagnostics may be more feasible to implement in LMICs. Diagnoses of gut dysbiosis or EED is often complex, typically requiring invasive, stool or urine tests.[36-38] Diagnosis of gut dysbiosis may also be based on symptoms, although this may be less accurate. Commonly this includes gastrointestinal symptoms such as bloating, diarrhea, constipation, abdominal pain or gas.[57] EED can often be asymptomatic.[48] Undernutrition is diagnosed with the use of standard measurements such as BMI or MUAC.[42,43]

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Clinical endpoint for licensure	Clinically important difference in improving maternal gut dysbiosis/EED.	Clinically important difference in improving maternal gut dysbiosis/EED or undernutrition. Clinically important difference in neonatal outcomes (e.g. birthweight, preterm birth) as a result of maternal gut dysbiosis, EED or undernutrition.	Clinical endpoints have been selected based on the indication of LBPs and probiotics to target gut dysbiosis and/or EED. Optimally, this also includes a reduction of maternal undernutrition.
Product format, administration, frequency, and dose	Oral administration, including capsules, tablets, powder, or gummies. Daily doses. Acceptable and tolerable dose. Can be administered during all trimesters of pregnancy and during lactation.	Oral administration, including capsules, tablets or gummies that do not require reconstitution with water or other additional ingredients. 1-2 doses per week. Acceptable and tolerable dose. Can be administered during all trimesters of pregnancy and during lactation.	Both probiotics and LBPs are most commonly administered orally when targeting the gut microbiome.[58,59] Oral administration would likely be acceptable and feasible in low- and middle-income countries where there may be limited resources to administer invasive intervention.
Drug interactions	No significant drug-drug interactions with common antenatal treatments (medicines or supplements) or with treatments used in women with undernutrition (such as nutrient	No drug-drug interactions with common antenatal treatments (medicines or supplements) or with treatments used in women with	The treatment must have minimal to no adverse interactions with drugs commonly used in pre-conception,

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	supplementation, fortified or supplementary foods), or drugs used for common comorbidities of gut dysbiosis.	undernutrition (such as nutrient supplementation, fortified or supplementary foods), or drugs used for common comorbidities of gut dysbiosis.	pregnant or postpartum women with gut dysbiosis, EED or undernutrition. Gut dysbiosis is believed to be associated with an increased risk of several conditions including inflammatory bowel disease, obesity, autoimmune diseases, type I and II diabetes, chronic kidney disease and mental health conditions.[60,61]
Treatment adherence	Frequency of discontinuation during therapy <20%.	Frequency of discontinuation during therapy <10%.	Treatment adherence rates can vary significantly depending on the intervention type. A dropout rate of 20% has been used in probiotic trial sample size calculations.[62] Lower discontinuation rates are important to avoid poor health outcomes.[63]
Stability / Shelf Life	Stable at 30°C. Easy to transport and store in a range of climatic conditions. 24-month shelf life as per product storage instructions.	Stable at 30°C. Easy to transport and store in a range of climatic conditions.	Products must be suitable for use in various temperature and climate conditions, particularly given the climate of many LMICs. Some probiotics and LBPs require cold chain, however increasingly

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	No requirement for cold chain.	3 to 5-year shelf life in climatic zone IVb (simulated with 30°C and 75% relative humidity). No requirement for cold chain.	products are being developed that are suitable for transport and storage at room temperature.[64,65]
Product Registration and Regulation	Approval from national regulatory agency in target country. <u>Probiotics:</u> Registration through either drug or supplement pathways. <u>Live biotherapeutic products:</u> Registration through drug pathway. Approval by at least one internationally recognized regulatory authority (e.g. USFDA, European Medicines Agency, Swissmed).	Approval from national regulatory agency in target country. <u>Probiotics:</u> Registration preferably through non-drug pathway. <u>Live biotherapeutic products:</u> Registration through drug pathway. Approval by multiple internationally recognized regulatory authority (e.g. USFDA, European Medicines Agency, Swissmed).	Probiotics would ideally be registered through a non-drug pathway to avoid the complexities associated with this pathway. Live biotherapeutic products would need to be registered through a drug pathway given their therapeutic nature.[29] All interventions should be approved by the national regulatory authority in the relevant country.
Product presentation	Easy to open and administer. Packaging must aim to protect and preserve the quality of the product and prevent damage during transport and storage.	Compact, lightweight, easy to open and administer. Packaging must aim to protect and preserve the quality of the product	Packaging that is easy to open and administer will aid in the implementation of these products.

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		and prevent damage during transport and storage. Environmental impact of the packaging should be minimized.	For LBPs, packaging and design must comply with regulatory guidance from a stringent regulatory authority or WHO standards for packaging for pharmaceutical products.[66]
Primary Target Delivery Channel	Appropriately trained health workers in a range of settings including: - Formal antenatal and postnatal services where pregnant women are receiving care. - Routine health facility services for women of reproductive age for pre-conception. - Nutrition programs targeting undernutrition. <u>Probiotics:</u> Additionally, non-health facility delivery channels such as community pharmacies or supermarkets.	Same as minimum	The intervention should be easily delivered in a range of health facilities, including local primary facilities. Both products would require suitably trained health professionals to diagnose EED or gut dysbiosis. Additionally, live biotherapeutic products would require suitably trained health professionals to prescribe a suitable LBP. In contrast, probiotics targeting women with undernutrition would not require a health professional to diagnose a specific condition beyond undernutrition, so could be delivered through other channels such as pharmacies, supermarkets, etc.

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Target Procurement Price	Products are affordable in the public sector in LMICS.	Products are affordable in the public sector in LMICS. Unit cost of products is similar to other treatments for women with gut dysbiosis, EED or undernutrition. Bulk purchase discounts available for organizations, nutrition programs or governments.	Affordability is an essential consideration, particularly given the burden of undernutrition in LMICs and limited resource settings.[15] Affordability is essential to individual consumers and for larger scale procurements by governments or organizations.
Expected financing sources	Procurement in LMICs financed by national governments, international agencies (including UN organizations), and/or international donors, or private sector.	Procurement financed by national governments or private sector.	Procurement of medicines for use in pregnancy, lactation and for women of reproductive age in LMICs varies between countries. It may include governments as well as support from international organizations, agencies or funders. Procurement of effective treatments for maternal gut dysbiosis and undernutrition would ideally be prioritized by national governments.
Volume estimates	Volumes compatible with incidence of gut dysbiosis and undernutrition in pregnant and	Same as minimum	There are currently no reliable global estimates of gut dysbiosis or EED in

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	lactating women, and women of reproductive age.		pregnant and lactating women, or women of reproductive age. The estimated prevalence of low BMI in women across Africa and Asia is upwards of 10%.[15] In Africa, malnutrition among pregnant women is estimated at 23.5%,[67] with rates in some areas significantly higher, including between 38% to 44.9% in several regions of Ethiopia.[68,69] As maternal gut dysbiosis is an emerging research area, there are currently no reliable global estimates on the coverage of probiotics and LBPs in the target populations.

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