

Grand Challenges in Global Health



Discover New Ways to Achieve Healthy Growth

Funding Opportunity Announcement

To prevent adverse developmental outcomes including: growth restriction, stunting, wasting, and impaired cognitive development during the first 1,000 days following conception in the developing world

Bill & Melinda Gates Foundation

**Global Health Discovery
and
Nutrition**

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1 INTRODUCTION

We are continuing the mission set forth in the Grand Challenges in Global Health initiative to overcome persistent bottlenecks in creating new approaches and interventions that can radically improve health in the developing world. Here we announce a new grant program within this initiative: Discover New Ways to Achieve Healthy Growth. This program seeks to prevent outcomes caused by the adverse effects that nutritional deficiencies, infections, and environmental toxins can have on healthy developmental processes including: growth restriction, stunting, wasting and impaired cognitive development during the first 1,000 days following conception (-9 to 24 months) in the developing world.

Note: Two related funding opportunities within the Grand Challenges in Global Health initiative are also being announced this fall: *Preventing Preterm Birth*¹ and *Biomarkers of Gastrointestinal (Gut) Function and Health*.² The *Preventing Preterm Birth* program aims to explore the underlying mechanisms leading to preterm birth or stillbirth (associated with preterm birth) with emphasis on the role of infection, inflammation, and poor nutrition. The objective of the *Biomarkers of Gut Function and Health* program is to identify and validate biomarkers that will be sensitive, quantitative indicators correlated with outcomes such as nutrient absorption, stunting, and cognitive development. Researchers with new ideas and approaches addressing either of these topics are encouraged to respond with submissions to the appropriate program; proposed activities that align with the goals of these related programs will be considered outside of the scope of the *Discover New Ways to Achieve Healthy Growth* program.

2 PROGRAM GOAL

The goal of this opportunity is to elucidate new pathways or mechanisms that will directly inform the development of interventions for the prevention of impaired growth, i.e. stunting and wasting, during the first 1,000 days following conception in the developing world. Ultimately we aim to identify simpler, less costly, and more effective interventions delivered before conception, during pregnancy, or in the first two years of life. To meet this goal, approaches should address the underlying biological mechanisms that lead to these adverse developmental outcomes focusing *specifically* on either or both infection and nutrition, the two primary factors involved in altering the course of fetal and infant growth and development in the developing world.

3 BACKGROUND

The concept of healthy growth and development in infants and young children has various definitions and has historically been gauged using anthropometric indicators³ in addition to other more recently established metrics including: birth weight and length, body-mass index, lean tissue composition, proportion and location of adipose tissue, organ development,⁴ and linear growth as a function of

¹ For more details, see the *Preventing Preterm Birth* funding opportunity at <http://www.grandchallenges.org/>

² For more details, see the *Biomarkers of Gastrointestinal Function and Health* funding opportunity at <http://www.grandchallenges.org/>

³ Widdowson EM. Harmony of Growth. *Lancet* 1970; 1(7653): 901-5.

age.^{5,6} An alternative definition utilizes a life course approach and views each phase of development as optimally preparing the child for the next phase of the life course.⁷

The growth and development of an organism, as described by Elsie Widdowson in *The Lancet* in 1970, is a, "... complex affair, involving a multitude of different processes working together in harmony..."³. This 'harmony of growth' concept encompasses the spatial and temporal coordination of tightly organized and highly regulated processes that allocate nutrients and guide the correct and proportional maturation of different tissue types and organs during healthy human development.⁵ Consequently, growth failure in early life, either in terms of height or weight gain, can reflect inadequate development and subsequent dysfunction of a wide range of organs and tissues. Indeed attainment of a certain physical stature is not a goal, in and of itself, but rather it is a proxy for the success of basic developmental processes.

Accumulating evidence indicates that the first 1,000 days following conception is a critical window of time when many of these crucial developmental processes occur. During the fetal period, the developmental environment, including available nutrients,⁸ hormonal signaling, and pathogen exposure *in utero*, may induce pathophysiological processes, including intrauterine growth restriction (IUGR) or less subtle alterations, which subsequently have serious negative consequences for health in infancy, childhood, and adulthood.^{6,8} An example of this linkage are studies that have shown the correlation between birth weight and size of the thymus⁹ which is, in turn, important for development of T-cell immune responses that can alter risk of infection-related mortality in infancy.¹⁰ Furthermore, recent evidence indicates that a major phase of human neurogenesis and neuronal migration occurs before 18 months of age;¹¹ it seems probable that those tissues exhibiting very rapid growth, including the neonatal brain, are most sensitive to insult.

At present, research in this area is hampered by a lack of collaborative efforts that engage scientists from a range of scientific and technological disciplines. Consequently, there are few broadly applicable preventative solutions or interventions for stunting and wasting during the first 1,000 days following conception. This situation is especially dire in the developing world. In 2005, 32% of children under the age of 5 in developing nations were estimated to be stunted, where the region-specific prevalence was

³ Widdowson EM. Harmony of Growth. *Lancet* 1970; 1(7653): 901-5.

⁴ Example of organ development: Assessment of infant nutrition on thymic development by Moore et al., 2009 *Acta Paediatr*

⁵ Jackson AA, Burdge GC, and Lillycrop KA. *J Nutrigenet Nutrigenomics* 2010; 3(4-6):192-208.

⁶ Gardner DS, Ozanne SE, and Sinclair KD. *Philos Trans R Soc Lond B Biol Sci* 2009; 364(1534):3419-27.

⁷ "Promoting Optimal Fetal Development: Report of a Technical Consultation." *World Health Organization, Nutrition for Health and Development/Making Pregnancy Safer/Evidence and Information for Policy* 2006.

⁸ Nutrients, also including micronutrients such as essential vitamins and provitamins, fatty acids, metals, and minerals (including nitrogen sources)

⁹ Moore SE, Prentice AM, Wagatsuma Y, Fulford AJ, Collinson AC, Ragib R, Vahter M, Persson LA, Arifeen SE. *Acta Paediatr.* 2009; 98(7): 1168-75.

¹⁰ Aaby P, Marx C, Trautner S, Rudaa D, Hasselbalch H, Jensen H, Lisse I. *Acta Paediatr.* 2002.; 91(6):698-703.

¹¹ Sanai N, Nguyen T, Ihrie RA, Mirzadeh Z, Tsai HH, Wong M, Gupta N, Berger MS, Huang E, Garcia-Verdugo JM, Rowitch DH, Alvarez-Buylla A. *Nature.* 2011; 478:382-7.

particularly high in Eastern Africa (50%) and South-Central Asia (41%).¹² In these regions of the world, uptake of other potential life-saving interventions aimed at the mother or infant were equally low. While investments in infrastructure, nutritional education, and other basic health services can overcome some of these barriers, there is an opportunity to create the next generation of interventions to improve lives at the ‘frontline’ of care. The particular need for novel interventions is highlighted by a report indicating that use of all known effective interventions (focused on supplementing the nutrition of pregnant mothers and infants and reducing the burden of malaria during pregnancy and helminth infections during infancy) in 99% of children would decrease the prevalence of stunting by only 1/3.¹³

Therefore there is an urgent need for a broad range of scientific studies to illuminate the burden, root causes, underlying molecular pathways and potential targets for interventions to improve fetal, newborn, and infant outcomes. Since many of these outcomes are caused by the adverse effects that infections, suboptimal nutrition, and toxins or chemicals found in the environment have on healthy developmental processes, mechanistic studies to inform the discovery or refining of better interventions relevant to the developing world is the ultimate goal of this solicitation.

4 PROGRAM OBJECTIVE AND SCOPE

Research efforts relevant to informing future interventions for treating or preventing growth restriction, stunting, or wasting may include the investigation of pathways or mechanisms: a) involved with the acquisition or metabolism of essential vitamins, minerals, fatty acids, or other nutrients; b) controlled by hormones or influenced by autonomic functions; c) induced by pathogens or immunological activity; or d) environmental toxins. The Discover New Ways to Achieve Healthy Growth program will address three developmental segments or age groups:

- 1) prenatal, including preconception factors as well as those during fetal development,
- 2) infants from birth to 6 months of age, and
- 3) infants from 6 to 24 months of age.

For each of these developmental segments, the program will be focused on mechanistic approaches to discover or inform the development of novel interventions and the capacity to monitor their effect at a mechanistic level to address infection, exposure to environmental toxins (e.g. aflatoxin), and/or nutritional insult that could induce the aforementioned adverse developmental outcomes. Additionally, for studies focused on the fetal period, mechanistic investigations to inform interventions addressing placental dysfunction or IUGR occurring between conception and birth can be considered.

Of special interest to the Bill & Melinda Gates Foundation is the *role of nutrition, infection, and certain environmental exposures* in the origins of stunting and wasting during the first 1,000 days following conception. While stunting and wasting are but a few of the many adverse growth and development-related outcomes faced by mothers and infants of the developing world, their primary importance is

¹² Black RE, Allen LH, Bhutta ZA, and Caulfield LE. *Lancet* 2008; 371: 243-60.

¹³ Bhutta ZA, Ahmed T, Black RE, Cousens S, Dewey K, Giugliani E, Haider BA, Kirkwood B, Morris SS, Sachdev HP, Shekar M. *Lancet* 2008; **371**: 417-40.

reinforced by: 1) the lack of existing widely applicable preventative solutions, 2) the broad applicability and particular relevance to developing world settings, 3) the likely overlap in causal exposures and biological mechanisms, and 4) the wide array of data and hypotheses available upon which to develop proof-of-concept studies for novel biological pathways leading to disease.

Collaboration: The aim of this initiative is to create a consortium of individually funded projects that will benefit from information sharing activities among its members. The collaborative nature of sharing experimental methods, data, and resources is intended to increase the efficiency of the overall effort to discover novel interventions for those that need them most in the developing world. The specific terms of the collaborative activities will be negotiated prior to the grant award.

Expected outcomes from this effort include *improved capability* to compare and validate local research findings with new or established cohorts, particularly important in low-resource settings. Activities that would be part of efforts include:

- **Cohort Harmonization:** When collaborating with or establishing new cohorts, investigators will be expected to participate, whenever possible, in cohort harmonization. Appropriate determination and classification of populations to be considered will be established to ensure effective focus of effort. Discover New Ways to Achieve Healthy Growth cohort sites will be expected to:
 - Develop and follow standard operating procedures and quality control protocols for specimen collections;
 - Participate in the establishment of a minimum common set of data and specimens collected across the Discover New Ways to Achieve Healthy Growth program.

- **Data Sharing:** Data generated through the Discover New Ways to Achieve Healthy Growth studies will be shared with the broader scientific community in accordance with the foundation's Global Health Data Access Principles (<http://www.gatesfoundation.org/global-health/Documents/data-access-principles.pdf>). A data sharing plan will be developed that is equitable, ethical and efficient, and will include:
 - A data share and publication policy;
 - A data use agreement;
 - Discover New Ways to Achieve Healthy Growth manuscript citation;
 - Acknowledgement of the core Discover New Ways to Achieve Healthy Growth investigators.

Characteristics of successful proposals: Successful proposals should address a hypothesis that lies along a critical path to practical, affordable, and scalable interventions. While these studies will ultimately be centered on analysis of samples from human cohorts, studies evaluating hypotheses first in laboratory or animal models are also encouraged as part of the collaboration. In the case of animal models, the relevance to human placentation, gestation or parturition should be clearly demonstrated. The studies proposed should be relevant to large at-risk populations in the developing world, enhancing the

potential for creating transformative solutions. The aims of the proposed studies should address well-defined hypotheses, the outcomes of which can be used to support the design of interventional trials.

What we are looking for: The goal of this program is to uncover the mechanistic basis of adverse developmental outcomes (including: growth restriction, stunting, wasting, and impaired cognitive development) induced by infection, suboptimal nutrition, and environmental toxins during the first 1,000 days following conception. The scope of proposed experimental work should provide evidence that the mechanism uncovered is relevant and applicable to a human or preclinical setting such that the knowledge gained will inform the future development of an intervention. Successful proposals may include one or more of the following components, among others:

- Determination of the pathophysiological changes (e.g. abnormal tissue and organ development) that define fetal stunting, insufficient development of immune function, deficiencies in neural or cognitive maturation, or the stunting and/or wasting of infants.
- Alteration of hormonal regulation in response to malnutrition, infection, or environmental exposure and linkage to functional effects of this change in hormonal signaling.
- Determination of mechanisms by which suboptimal growth may be influenced by cellular processes or factors involved in cell differentiation including DNA methylation, histone modification, or regulation by microRNAs.
- Elucidation of the importance of different mechanisms for the regulation of growth or the processes by which growth failure may occur during the different stages of fetal development.
- Determination of the mechanisms which influence immune responses to pathogens and response to immunization in stunted and wasted newborns and infants.
- Defining the causal relationship (and mechanisms underlying this relationship) between infection, microbial ecology, and inflammation during pregnancy that lead to the pathophysiological changes (such as placental malformation or abnormal vascular function) that characterize unhealthy growth.
- Comprehensive analysis of micro- and macro- nutrients and the mechanisms by which nutritional imbalances change fetal and neonatal physiology and may result in stunting and wasting, or alternatively, elucidation of mechanisms by which specific sets of nutrients may promote healthy growth including but not limited to:
 - Determination of the link between micronutrient status and mechanistic effectors (e.g. folate, betaine, choline, zinc, essential amino acids, fatty acids, etc and associated cellular receptors and effectors);
 - Determination of the effects of maternal exposure to toxins (and their dosage and duration) common to the developing world (e.g. aflatoxin);
 - Mechanistic determination of the physiological processes that are affected by specific sets of nutrients in particular foods (e.g. milk) that appear to have growth-promoting effects during the first 1,000 days following conception.

- Investigation of already completed clinical or preclinical trials in order to understand specific mechanisms that underlie a successful response to prevention or treatment of stunting and wasting.
- Determination of mechanisms based on knowledge from veterinary science or animal husbandry for the prevention or treatment of poor placentation, stunting or wasting;
- Other studies of specific hypotheses related to the intersection of nutrition, environmental exposures, and infectious disease relating to stunting and wasting.
- Development of technologies or new methods appropriate to address issues of stunting and/or wasting in developing world settings.

Proposals we will not consider for funding: We will not consider proposals with hypotheses addressing effects that are not *specifically* relevant to, mediated by, or resulting from infectious diseases, nutritional deficiency, or environmental exposures in low resource settings. We will also not consider studies that answer basic science questions only (e.g. studies that lead to further hypothesis generation without providing knowledge that can provide a clear and informative path to development and testing of potential solutions), studies lacking analytic methods to provide a causal link between exposures of interest and specific mechanisms that lead to adverse outcomes, and studies which lead to solutions applicable to only a small portion of an affected population.

Proposed activities aligned with the goals of the two related RFPs mentioned in the introductory section fall **outside** the scope of this program. This would include research efforts that are focused on: 1) the exploration of the underlying mechanisms leading to preterm birth or stillbirth (associated with preterm birth) with emphasis upon the role of infection, inflammation, and poor nutrition;¹⁴ and 2) identification and validation of biomarkers that will be sensitive, quantitative indicators that can be correlated with outcomes such as nutrient absorption, stunting, and cognitive development.¹⁵ Proposers should use their best judgment and understanding of the three related programs to respond to the opportunity that most directly relates to their idea and approach.

What we are not looking for:

- Clinical trials testing specific interventions.
- Studies that measure associations between levels of single micro- or macro-nutrients in relationship to IUGR, stunting, and wasting.
- Epidemiological studies that solely investigate associations between infection, nutrients, or an environmental exposure with pregnancy outcomes rather than the analysis of the mechanistic basis for an association.

¹⁴ For more details, see the *Preventing Preterm Birth* funding opportunity at <http://www.grandchallenges.org>

¹⁵ For more details, see the *Biomarkers of Gut Function and Health* funding opportunity at <http://www.grandchallenges.org/>

- Studies that suggest interventions that do not provide an overall benefit for mother and/or child such as: inappropriate early cessation of breast feeding, interventions detracting from or disrupting routine immunizations or the Expanded Program on Immunization (EPI), etc.
- Studies that would ultimately lead to an intervention not applicable to a developing world setting.

5 PROGRAM STRUCTURE

The Bill & Melinda Gates Foundation is willing to fund up to a total of \$15M for research activities to uncover new pathways or mechanisms that will directly inform the development of interventions for the prevention of impaired growth during the first 1,000 days following conception in the developing world as part of this program. Proposals for funding are eligible for up to \$2,000,000 total cost per project in funding. Individual program budgets should be representative of the scope and magnitude of the proposed studies. The proposal should clearly identify decision points and endpoints that will fit within the proposed budget and time frame of 36 to 48 months. A Hard Milestone at 24 months will separate Part 1: Exploration and Mechanistic Understanding, and Part 2: Mechanism and Relevance to an Intervention. The activities of Part 1 should detail preliminary evidence for a mechanistic basis of the processes or pathways in question enabling the investigation to proceed to an expanded experimental system (animal models, validation in human cohorts, additional human populations) in Part 2. The scope of experimental work in Part 2 should provide evidence that the mechanism uncovered is relevant and applicable to a human or preclinical setting such that the knowledge gained would inform the future development of an intervention.

Allocation of funding will depend on a number of factors, including: relevance of the proposed work to uncover pathways or mechanisms that would inform the development of interventions to prevent stunting and wasting during the first 1,000 days following conception; the potential that such an intervention would be relevant to low-resource settings and would address problems faced by individuals in the developing world; scientific innovation and merit; and clarity of the work plan, including defined milestones (minimally a Hard Milestone at 24 months must be defined) and decision points. Specific milestones will need to be completed by 24 months as evidence of progress towards the goal of the initiative. The accomplishment of these milestones will allow an Executive Committee, composed of representatives from the Bill & Melinda Gates Foundation and external advisors, to examine the entire research portfolio and make adjustments as needed.

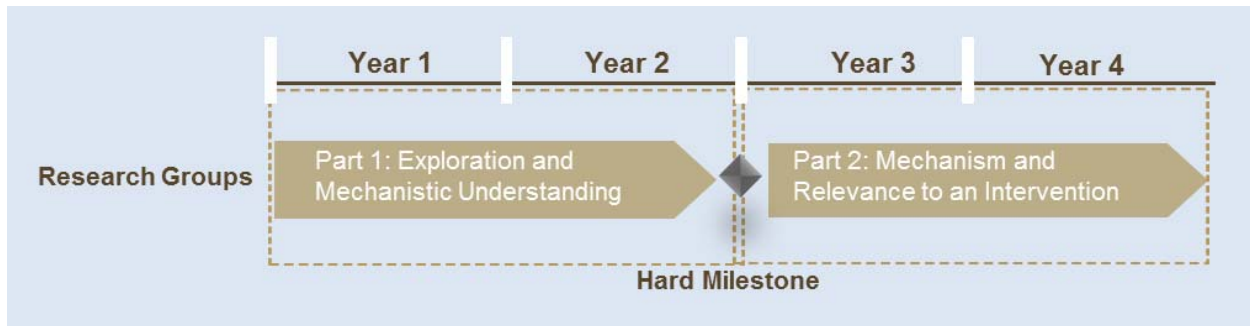


Figure 1. Program Structure with Illustrative Timeline

The Executive Committee will evaluate each project at that time to consider:

1. Deliverable accomplishments and evaluation of all project milestones including level of collaboration with other investigators within the initiative;
2. Decisions on redirecting projects at 24 months and from annual reviews;
3. Potential need for budgetary modifications based on project achievements at 24 month evaluation and at annual reviews;
4. Potential withdrawal of funding if any project is not meeting milestones and deliverables or if hypotheses and aims of any specific project are not resulting in expected outcomes towards a translatable discovery;
5. Potential realignment of each project with the program objective;
6. Likelihood of achieving objectives in subsequent years.

6 RULES AND GUIDELINES

6.1 Application Instructions and Review Process

A Letter of Inquiry (LOI) in response to this RFP should be submitted no later than January 25, 2012 10:00 AM PST. The Bill & Melinda Gates Foundation (which may subsequently be referred to as ‘the Gates Foundation’ or ‘the foundation’) will evaluate the LOIs and applicants who have projects of further interest to the Gates Foundation will be invited in March 2012 to submit a full proposal in April 2012. These time periods are subject to change. All applicants will be notified by email in a timely manner of any change to the dates for notification and proposal deadline. Instructions on the preparation of full proposals will be provided to selected applicants. Due to expected high volumes, the Gates Foundation will not be able to provide individual feedback for LOIs not selected to submit full proposals. The foundation may use external reviewers to assess the merit of proposals; final selection decisions will be made by the foundation. An invitation to submit a proposal does not guarantee that the foundation will award a grant to the applicant. The foundation may amend or cancel this RFP at any time.

LOIs must be submitted electronically, using the forms and process described at the following address <http://www.grandchallenges.org/GrantOpportunities/Pages/healthygrowth.aspx>

The following schedule lists important deadlines and is subject to change:

Table 1 Application Schedule

Key Dates and Deadlines	Events
November 7, 2011	System open to accept Letters of Inquiry (LOIs)
January 25, 2012 10:00 AM PST	Application deadline for LOIs
March 2012	Invitation for submission of full proposals
April 2012	Application deadline for full proposal

6.2 Evaluation Criteria

Significance. Is the approach likely to dramatically add to knowledge about the causative mechanisms and the development of potential interventions for stunting and wasting of infants? Do the assays, technologies, and systems for analysis proposed have broad applicability to solve the problem?

Approach. Are the conceptual framework, design, methods, and analyses innovative, adequately developed, well integrated, and appropriate to the aims of the proposal? Do the approaches or methods scale in a manner consistent with the overall goals of this request for proposals (RFP)? Does the proposal acknowledge potential problem areas and consider alternative tactics? Is the likelihood of successful project completion high? Are the proposed timelines and interim milestones and the hard milestone (end of year 2) appropriate, feasible, and technically sound?

Organizational and Investigator Capability. Is the research team appropriately trained, experienced, and positioned to carry out this work? Is there strong evidence of substantive organizational capability and commitment? Does the environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environments including partnerships with industry or employ useful collaborative arrangements? Are collaborative arrangements already in place?

Willingness to Collaborate. Are the applicants, including all sub-contractors, willing to collaborate and share experimental methods, data, and resources among the other independently-funded members of the Discover New Ways to Achieve Healthy Growth consortium?

Environment. Does the environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environments including partnerships with industry or employ useful collaborative arrangements? Is there adequate evidence of institutional support?

Best Value. Proposals will be evaluated for the cost of the proposed effort relative to the complexity of the proposed work and the degree of risk and advancement proposed. Proposals that have execution plans which represent particularly thoughtful and efficient use of resources will be preferred over proposals representing comparable efforts that do not represent the same value for the investment.

Additional review criterion. In addition to the above criteria, proposals will also be reviewed with respect to the adequacy of the proposed protection for animals and humans, to the extent they may be adversely affected by the project proposed in the application.

6.3 Eligibility Criteria

Applicant organizations must be individual non-profit organizations, for-profit companies or other recognized institutions that can successfully execute the activities in their technical area.

6.4 Allowable Costs

Grant funds may be used for the following costs. Please provide budget estimates according to these categories: personnel; required travel; supplies; contracted services; sub-grants and consultants. Partial or full support for equipment may be requested subject to the following circumstances. Use of any equipment purchased with grant funds is limited by law to charitable purposes for the depreciable life of the equipment. Please note that for many non- U.S. entities, U.S. tax law considerations may affect whether the Bill & Melinda Gates Foundation will permit purchase of equipment with a depreciable life that is greater than the grant period being requested. In such cases, leasing would be preferable.

Indirect costs: The Bill & Melinda Gates Foundation provides limited indirect cost in accordance with its policy. Prior to submitting an LOI, please review the foundation's indirect cost policy at http://www.gatesfoundation.org/grantseeker/Documents/Indirect_Cost_Policy.pdf

Travel funds are required to participate in one RFP-related meeting per year for up to 4 key members of the project team. Meetings will possibly be held at an international venue.

6.5 Privacy Notice

To help The Bill & Melinda Gates Foundation staff in their evaluation and analysis of projects, all proposals, documents, communications, and associated materials submitted to the Bill & Melinda Gates Foundation (collectively, "Submission Materials") will become the property of the Bill & Melinda Gates Foundation and may be subject to external review by independent subject matter experts and potential co-funders in addition to analysis by the Bill & Melinda Gates Foundation staff. Please carefully consider the information included in the Submission Materials. If you have any doubts about the wisdom of disclosure of confidential or proprietary information, the Bill & Melinda Gates Foundation recommends you consult with your legal counsel and take any steps you deem necessary to protect your intellectual property. You may wish to consider whether such information is critical for evaluating the submission, and whether more general, non-confidential information may be adequate as an alternative for these purposes.

We respect confidential information we receive. Nonetheless, notwithstanding your characterization of any information as being confidential, the Bill & Melinda Gates Foundation may publicly disclose all

information contained in Submission Materials to the extent as may be required by law and as is necessary for potential co-funders and external reviewers, such as government entities, to evaluate them and the manner and scope of potential funding consistent with appropriate regulations and their internal guidelines and policies.

6.6 Warranty

By providing any Submission Materials, the sender warrants the Bill & Melinda Gates Foundation that they have the right to provide the information submitted. Applicants with questions concerning the contents of their Submission Materials may contact the Bill & Melinda Gates Foundation at: grandchallenges@gatesfoundation.org

6.7 Intellectual Property

Since the output of this program may lead to innovative technologies and/or products that could result in improved diagnostics or interventions ('products', intellectual or otherwise, which may include, but are not exclusively defined as: devices, drug or nutraceutical formulations, biologics, or patentable processes or approaches) for those that need of them most in the developing world, the successful development of these high priority products may require substantial involvement and support of private sector industries as sub-contractors, and may also involve collaborations with multiple organizations, including academic and/or non-profit research institutions. It is the intent of this program to support the formation of appropriate public-private partnerships that are essential to meet these urgent global health needs. Intellectual property (IP) rights and the management of IP rights are likely to play an important role in achieving the ultimate goals of this initiative. To this end, the foundation requires that, even at the LOI stage, all applicants seriously consider their willingness to submit a full proposal in compliance with the foundation's proposal guidelines, a portion of which asks for certain information and intentions regarding intellectual property and global access concerns. Specifically, the Bill & Melinda Gates Foundation requires that you agree to use good faith efforts to conduct and manage the research, technologies, information and innovations involved in the Project in a manner that enables (a) the knowledge gained during the Project to be promptly and broadly disseminated, and (b) the intended product(s) to be made available and accessible at reasonable cost to the developing countries of the world. The foundation refers to this as "Global Access."

As part of the foundation's review and evaluation of each full proposal, due diligence will be conducted with respect to each participant's ability and commitment to manage intellectual property in a manner consistent with the stated scientific and charitable goals of the Bill & Melinda Gates Foundation. Due diligence activities may include inquiry into an applicant's:

- 1) Freedom to operate (FTO) and ability to freely use and acquire needed background technology;
- 2) Commitment to promote the utilization, commercialization and availability of inventions for public benefit in developing countries

In order to facilitate this due diligence process applicants are encouraged to provide information with respect to the items above in their submission materials. Applicants should consider whether the

protection through IP (in particular through patents) new pathways or mechanisms that will directly inform the development of interventions would best further the goals of this project to improve the health and development of children in the developing world. To be clear, the goal is not to develop a position for or against such IP, but to articulate the role that IP would play in furthering the specific goals of this project.

Applicants will be required to prepare a Global Access Strategy reflecting how they will achieve the Global Access requirements described above.

Applicants are also expected to make new information and materials known to the research and medical communities in a timely manner through publications, web announcements, progress reports to the foundation, and other appropriate mechanisms. These concepts may be discussed at some length with the applicants invited to submit full proposals, and will be addressed (to the extent appropriate) within each final grant agreement. The Global Access Strategy will also include provisions defining these concepts.

7 RESEARCH ASSURANCES

While not necessary for the LOI, as applicable to the individual project, the Bill & Melinda Gates Foundation will require that for each venue in which any part of the project is conducted (either by your organization or a subgrantee or subcontractor) all legal and regulatory approvals for the activities being conducted will be obtained in advance of commencing the regulated activity. The foundation will further require you to agree that no funds will be expended to enroll human subjects until the necessary regulatory and ethical bodies' approvals are obtained.

7.1 Data Access Principles

In accordance with its charitable mission, the foundation is committed to optimizing the use of health-related data to translate knowledge into life-saving interventions. To this end, it is essential that data are made widely and rapidly available to the broader global health community through good data access practices.

Data access is intended to promote:

- *Innovation*, by encouraging diversity of analysis and opinion, facilitating evaluation of alternative hypotheses, permitting meta-analysis, and facilitating synthesis of results from individual projects into a larger whole, thereby promoting potentially lifesaving new insights.
- *Collaboration*, between teams and institutions, and among diverse disciplines, resulting in greater productivity and creativity.
- *Efficiency*, by preventing unnecessary duplication of effort, enabling secondary analyses of existing data, and enabling the redirection of resources to the most promising research endeavors, thereby maximizing the potential impact of investments.
- *Accountability*, by encouraging independent verification and analysis, thereby improving data quality

- *Capacity Strengthening*, by facilitating the education of new researchers and evaluators and enabling broader access to data for secondary analysis, which is of particular importance to investigators in developing countries.

7.2 Research Involving Human Subjects

You agree that no funds will be expended to enroll human subjects in any research project subject to Institution Review Board (IRB) or independent ethics committee (IEC) approval until such approval has been obtained for each site (see below sections for more information).

7.3 Research Involving Animals

You agree that no funds will be expended on studies involving animals until all requisite approvals are in place for each site (see below sections for more information). For purposes of this provision, an “animal” is defined as any live, vertebrate animal used or intended for use in research, research training, experimentation, biological testing or for related purposes.

7.4 Clinical Trials

Projects in the Discover New Ways to Achieve Healthy Growth program may require clinical trials on human subjects; a condition of this grant is your agreement that the appropriate Institutional Review Boards (“IRBs”) and ethical committees will review and approve the clinical protocols prior to trial initiation. You further agree to conduct clinical trials associated with the project under the generally accepted principles of “Good Clinical Practices” as defined by the International Conference on Harmonization (ICH) E-6 Standard, the United States Food and Drug Administration (FDA) or the European Agency for the Evaluation of Medicinal Products (EMA), as applicable. You acknowledge and agree that, as between you and the foundation, you take and will have full responsibility for all compliance, data safety, monitoring, and audit requirements of the relevant regulatory agencies, both for yourself and all other sites included in the project, including those activities conducted through subgrants, subcontracts or other collaborative efforts. You acknowledge and agree that any activities by the foundation as the grantor funding the Project, including its review of the Proposal or suggested modifications to the Project, does not modify the provisions of this paragraph or constitute the basis for any claim by you against the foundation.

7.5 Indemnification

For all clinical trials, the foundation requires that you agree to indemnify, defend and hold the foundation harmless from and against any and all liability, loss, and expense (including reasonable attorneys’ fees and expenses) or claims for injury or damages arising out of or resulting from, or that are alleged to arise out of or result from, the actions or omissions by you or of any of your officers, agents, employees, subgrantees, contractors or subcontractors with respect to the grant. You agree that any activities by the foundation in connection with the Project, such as its review or proposal of suggested modifications to the Project, will not modify or waive the foundation's rights under this paragraph.

7.6 Coverage for all Sites

You agree that for each venue in which any part of the Project is conducted (either by your organization or a subgrantee or subcontractor) all legal and regulatory approvals for the activities being conducted will be obtained in advance of commencing the regulated activity. You further specifically agree that no funds will be expended to enroll human subjects until the necessary regulatory and ethical bodies' approvals are obtained.

7.7 Regulated Activities

The coverage requirements set forth in the preceding paragraph include but are not limited to regulations relating to: research involving human subjects; clinical trials, including management of data confidentiality; research involving animals; research using substances or organisms classified as Select Agents by the U.S. Government; use or release of genetically modified organisms; research use of recombinant DNA; and/or use of any organism, substance or material considered to be a biohazard, including adherence to all applicable standards for transport of specimens, both locally and internationally, as appropriate. As applicable, regulated activities and their documentation are to be conducted under the applicable international, national, and local standards. Documentation of research results should be consistent with regulations and the need to establish corroborated dates of invention and reduction to practice with respect to inventions where this is relevant.

7.8 Institutional Review Board (IRB) Approval

You agree to obtain the review and approval of all final protocols by the appropriate IRBs and ethical committees prior to enrollment of the first human subject and when using human material. A similar provision applies to Institutional Animal Care and Use Committee approval of studies involving animals, and Institutional Biosafety Committee for biohazards and recombinant DNA. You agree to provide prompt notice to the foundation if the facts and circumstances change regarding the approval status of the IRBs or ethical committees for any final protocol(s).

7.9 Provision of Care for Human Subjects Research

In keeping with "Good Clinical Practice" standards, you will disclose to subjects and the IRBs what care and/or referrals will be available through participation in the study. Institutional policies regarding what care will be provided to personnel who are injured as a result of their work on the Project should similarly be developed, approved and implemented with notice to the employees.

7.10 Use of Animals in Research

You agree to be responsible for the humane care and treatment of animals in projects supported in part or whole by Gates Foundation funds; and to adhere to the official guidelines for animal research applicable in the country and locality where the trial is being conducted. No grant funds may be expended on studies involving animals until all requisite approvals are in place, and notification to that effect has been provided to the foundation. For purposes of this provision, an "animal" is defined as any live, vertebrate animal used or intended for use in research, research training, experimentation, biological testing or for related purposes. In the case of multi-national collaborations, the standards of each country may be followed, as long as (i) differences do not interfere with the design and analysis of

the Project, and (ii) regulations in your institution and host country do not conflict with the management of the Project.

You agree to take responsibility for compliance of all subgrantees or subcontractors (if any) with the appropriate animal welfare laws, rules and regulations. You must report annually as a part of your progress report that the activities are being conducted in accordance with applicable laws in each respective venue (e.g., U.S. grantees must use the U.S. Public Health Service standards. Non-U.S. grantees may cite national laws or the CIOMS International Guiding Principles for Biomedical Research Involving Animals (see http://www.cioms.ch/publications/guidelines/1985_texts_of_guidelines.htm) if there is not a relevant national standard.