



# Preventing Preterm Birth Initiative

## Exploring Pathways to Prevent Prematurity and Stillbirth

**Sponsored in partnership by:**

**Global Alliance to Prevent Prematurity and Stillbirth  
(GAPPS), an initiative of Seattle Children's,  
and  
Bill & Melinda Gates Foundation**

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# 1 INTRODUCTION

## Challenge Statement

To discover and develop novel interventions for prevention of preterm birth and stillbirth associated with preterm birth through rigorous analysis of underlying biological mechanisms that lead to these adverse outcomes, focusing on the roles of infection, inflammation, and nutrition in altering the course of pregnancy in the developing world.

## State of the field

Accumulating evidence suggests that poor maternal and fetal health set in motion an irreversible trajectory with serious negative consequences for health in infancy, childhood, and adulthood. At present, research to guide the discovery and development of pregnancy and perinatal interventions is hampered by a lack of collaborative, global efforts that engage scientists from a range of scientific and technological disciplines.

As a consequence, there are few broadly applicable preventative and therapeutic solutions for major adverse pregnancy outcomes such as preterm birth<sup>1</sup> (PTB) and stillbirth<sup>2</sup> (SB) – conditions that contribute directly and indirectly to an estimated 3.3 million deaths worldwide every year.<sup>3</sup>

Preterm birth and stillbirth likely share many common pathways and mechanisms. In high-income countries, 80% of stillbirths are delivered preterm.<sup>4</sup> The situation is especially dire in the developing world where 99% of the approximately 4 million perinatal deaths occur.<sup>5</sup> Sub-Saharan Africa and South Asia in particular have the highest maternal, fetal, and neonatal mortality rates and the lowest use of hospitals for delivery or newborn care. In these regions, the adoption of other potentially life-saving interventions aimed at the mother or infant are equally low. While investments in infrastructure, transportation, and other basic health services can overcome some of these barriers, there is an opportunity to create the next generation of medical technologies to save lives at the ‘frontline’ of care. The particular need for better understanding of the etiologies of PTB and SB and novel interventions is further supported by multiple studies suggesting that even if existing preventive interventions were fully scaled, fewer than 20% of PTB and 35% of SB would be prevented.<sup>6,7</sup>

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<sup>1</sup> Birth before 37 weeks of gestation, “very preterm” can refer to birth at less than 32 weeks gestation and moderately preterm can refer to 32-36 weeks gestation

<sup>2</sup> Colloquial term used inconsistently, typically refers to early (after 22 weeks) or late (after 28 weeks) fetal death

<sup>3</sup> Oestergaard MZ, Inoue M, Yoshida S, Mahanani WR, Gore FM, Cousens S, et al. Neonatal mortality levels for 193 countries in 2009 with trends since 1990: A systematic analysis of progress, projections, and priorities. *PLOS Medicine* 2011;8:e1001080.

<sup>4</sup> Flenady V, Middleton P, Smith GC, Duck W, Erwich JJ, Khong TY, et al. Stillbirths: the way forward in high-income countries. *Lancet* 2011;377:1703-17.

<sup>5</sup> Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: When? Where? Why? *Lancet* 2005; 365 (9462):891-900

<sup>6</sup> Simmons LE, Ruben CE, Darmstadt GL, Gravett, MG. Preventing preterm birth and neonatal mortality: exploring the epidemiology, causes, and interventions. *Semin Perinatol.* 2010;34:408-15.

<sup>7</sup> Bhutta ZA, Yakoob MY, Lawn JE, Rizivi A, Fridberg IK, Weissmna E, et al. Stillbirths: what difference can we make and what costs? *Lancet.* 2011;377:1523-38.

Therefore, there is an urgent need for a broad range of scientific studies to illuminate the root causes, underlying molecular pathways and potential targets for future interventions to improve pregnancy, fetal, and newborn outcomes. Furthermore, such studies must be integrated and coordinated to reflect the dynamic processes that result in a continuum of maternal, fetal, and neonatal health outcomes, especially in the context of populations where adverse outcomes are prevalent.

## 2 PROGRAM GOALS

*“Few biological processes as central to the survival of a species as parturition are so incompletely understood” – Romero et al. 2002*

This concise, yet powerful statement is unfortunately equally as true today as when it was first published almost a decade ago. Research to advance understanding of pregnancy and perinatal health remains globally underfunded, leading to inadequate effort being applied to understand normal pregnancy and its perturbations.

### Request for Proposals

The present Request for Proposals (RFP) is meant to catalyze additional research on preterm birth and stillbirth associated with preterm birth, including attracting investigators new to the field of reproductive sciences. While these conditions are but a few of the number of adverse pregnancy outcomes, their primary importance is 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, (4) the wide array of data and hypotheses available upon which to develop proof-of-concept studies for novel pathways and interventions; and (5) the compelling burden of disease globally.

### The primary goals of this RFP are to:

1. Explore underlying mechanisms leading to preterm birth or stillbirth (associated with preterm birth) with emphasis on the role of infection, inflammation, and poor nutrition.
2. Complete funded studies within three to four years that provide critical discoveries and evidence to guide development and testing of new interventions or refine the application of existing interventions. Support for clinical trials will not be provided in the context of this RFP. It is expected that studies funded in this RFP will illuminate potential targets based on basic causes and mechanisms for new intervention development focused on prevention in future clinical trials.

These primary goals are in support of a broader plan to bring new investigators, novel technologies, and global attention to the field of maternal, neonatal, and child health. Projects may include relevant

animal models or *in-vitro* studies. Ultimately, we envision the establishment of collaborative networks of researchers in high-burden settings. We expect these collaborations to offer open and broad-based sharing of specimens, research approaches, protocols, and data essential to discovery studies.

***Studies funded through this initiative are intended specifically to explore gestational origins, biological mechanisms and immunological responses to infection, inflammation, or nutritional conditions, which may include some environmental exposures that lead to preterm birth and/or stillbirth.***

***The goal of this initiative is to encourage scientific studies that eventually will lead to or refine preventive interventions for PTB and SB related to preterm birth, primarily in developing world settings.***

**Note:**

Two related funding opportunities within the Grand Challenges in Global Health initiative are also being announced this fall: *Discover New Ways to Achieve Healthy Growth* (<http://www.grandchallenges.org/ImproveNutrition/Topics/Pages/NutritionforInfantsandChildrenRound8.aspx>) and *Biomarkers of Gastrointestinal (Gut) Function and Health*

([http://www.grandchallenges.org/GCGHDocs/Gut\\_Function\\_Biomarkers\\_Rules\\_and\\_Guidelines.pdf](http://www.grandchallenges.org/GCGHDocs/Gut_Function_Biomarkers_Rules_and_Guidelines.pdf)).

The *Healthy Growth* program aims to discover novel interventions, or elucidate new pathways or mechanisms that will directly inform the development of interventions to prevent stunting and wasting during the first 1000 days following conception in the developing world. The objective of the *Biomarkers of Gut Function and Health* program is to identify and validate biomarker(s), or signatures of biomarkers that will be sensitive, as quantitative indicators that can be correlated with outcomes such as nutrient absorption, stunting, and cognitive development. Proposers with new ideas and approaches addressing either of these other topics are encouraged to respond with submissions to the appropriate program; proposed scientific projects that are more aligned with the goals of these related programs will be outside of the scope of the *Preventing Preterm Birth* program.

### **3 TOPIC AREA:**

***Preventing Preterm Birth (PPB): Explore gestational origins, biological mechanisms, and immunological responses to infection, inflammation, or nutritional conditions that lead to preterm birth and/or stillbirth associated with preterm birth.***

Emerging science is building a solid case linking maternal infection(s), nutrition, and certain environmental exposures with PTB and SB. However, numerous questions remain regarding which specific exposures are causal and the most relevant, which interventions may be the most efficacious for any particular population at risk, whom to target with any new or existing interventions, and the critical timing during gestation and fetal development that determines how to target those at risk for any

particular intervention. At the root of these issues is the need to understand the mechanistic basis (e.g., the molecular pathways and physiologic changes) that mediate preterm birth and stillbirth in the context of infectious disease, inflammatory responses, and nutritional deficiency.

### **Characteristics of successful proposals**

The goal is to complete scientific studies that eventually will lead to or refine preventive interventions for PTB and SB related to preterm birth, primarily in developing world settings.

Successful proposals should address a hypothesis that lies along a critical path to practical, affordable, and scalable interventions to prevent preterm birth or stillbirth. *While these studies will ultimately be centered on analysis of samples from human cohorts, studies evaluating hypotheses first in cellular or animal models are also encouraged.* In the case of animal models, the relevance to human placentation, gestation or parturition should be clearly demonstrated. Investigational approaches to identify causes, pathways, or mechanisms should be directed towards prevention of disease, as opposed to treatment of established disease. The studies proposed should be relevant to large at-risk populations within affected developing world populations, enhancing the potential for translational solutions that are well suited to implementation in the developing world. The aims of the proposed studies should address hypotheses, the outcomes of which can be used to inform pre-clinical development strategies, and ultimately focus and support the design of interventional trials.

### **Successful proposals may include one or more of the following components, among others:**

1. Evaluation of the causal or mechanistic linkage between infection/inflammation, microbial ecology, and immunity during pregnancy and the pathways and physiological changes that lead to PTB and SB. These may include, but are not limited to:
  - a. Determination of the microbiology and associated shifts in microbiota and in host factors that predispose to PTB and SB.
  - b. Determination of the immunologic responses and profiles associated with maternal and/or fetal infections (such as malaria, helminth infections, acute microbial infections, altered female reproductive tract microbiota, etc.) that are critically involved in PTB and SB.
2. Comprehensive analyses of micro- and macro- nutrients, nutritional biomarkers, and the identification of the mechanisms by which nutrition influences fetal and maternal physiology in ways that may promote PTB and SB.
3. Evaluation of the effect of duration and degree of maternal exposure to adverse environmental conditions (such as household air pollution or exposure to environmental toxins) in the developing world that generate risk of PTB and SB.
4. Other studies of specific hypotheses related to infectious agents and/or conditions, pre-pregnancy health conditions that impact fetal development, or environmental exposure that could lead to a better understanding of risk and mechanisms leading to PTB and SB, will also be considered.
5. Studies utilizing human cohorts, particularly from low and middle-income countries, are encouraged, and encouraged to follow commonly adopted standard operating procedures

for prospective specimen collection. Any research consortium agreement with investigators will be negotiated as part of the grant itself and specifics regarding data sharing and collaboration should be detailed in the proposal. Data sharing should comply with established formats and protocols.

**Proposals we will not consider for funding:**

We will not consider proposals that address hypotheses that are not *particularly* relevant to, mediated by, or resulting from infectious diseases, nutritional deficiency, or environmental exposures in low-resource settings. We will also not consider projects 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, studies which lead to solutions applicable to only a small portion of an affected population, studies which lead to solutions applicable only to the developed world, or proposals that fail to demonstrate willingness and ability to participate in sharing results, data, and other forms of collaboration.

**Specifically, we will not accept proposals that:**

1. Test specific interventions independent of linkage to mechanistic pathways.
2. Determine the relationships among PTB, SB and environmental exposures not relevant to the developing world.
3. Study linkages between mental health and PTB (e.g., depression and stress).
4. Investigate only the simple associations between infection and pregnancy outcomes rather than providing findings that determine the biological basis and mechanistic pathways necessary to establish rational and efficacious interventions.

## **4 PROGRAM STRUCTURE**

### **4.1 Participants**

We expect to fund a diverse group of investigators with skills and innovative approaches who will ultimately work together to interrogate hypotheses using state-of-the-art model systems. Collaboration and cooperation among Research Investigators will be strongly encouraged with preference for cross-disciplinary studies that could provide the most detailed interrogation of hypotheses, validation, and interventions appropriate to low-resource settings.

### **4.2 Program Phases**

The projects will be funded for a total of 3 to 4 years, based on project scope and progress, and separated into two phases:

1. *Early Testing and Exploration.* Projects during Phase 1 will begin experimentation addressing their hypotheses, including implementation of collaborative studies. Phase 1 would most likely take up to the first two years of the project period, but can extend into the 3<sup>rd</sup> year.
2. *Assessment of Translational Potential.* The goal of Phase 2 is to assess translational relevance of data from phase 1 using human data and samples. Investigators will be encouraged to share data, and utilize existing cohorts or biobanks to validate experimental studies. Emphasis on collaboration with existing cohorts or biobanks from the developing world and from high-burden settings is preferable. It is expected that the research begun in Phase 1 will continue in Phase 2.

Specific milestones proposed in Phase 1 will need to be completed at 24 months into the program as evidence of progress towards the initiative. The accomplishment of these milestones will allow the PPB Executive Committee (see Section 5.1) to examine the research portfolio and make adjustments as needed.

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. Guide decisions on redirection of all projects at 24 months and from annual reviews;
3. Determine need for budgetary modifications based on project achievements at 24 months evaluation and at annual reviews
4. Oversee 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. Continued alignment of each project with the program objective
6. Likelihood of achieving objectives in subsequent years
7. Oversees assurance that sub-awardees are moving results of discovery projects to early pre-clinical development when appropriate.

#### **4.2.1 Collaboration and Harmonization of Activities**

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:



1. **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. PPB cohort sites will be expected to:
  - a. develop and follow standard operating procedures (SOPs) and quality control protocols for specimen collections that utilize pregnancy cohorts
  - b. participate in establishment of a minimum common set of data and specimens collected across the PPB.
2. **Data Sharing:** Data generated through the PPB 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. a data sharing and publication policy
  - b. data use agreement
  - c. PPB manuscript citation
  - d. acknowledgement of the core PPB investigators.

## 5 RULES AND GUIDELINES

### 5.1 Program Direction

To oversee program management, an Executive Committee will be formed with representation from GAPPs, the Bill and Melinda Gates Foundation (the foundation), and two or three outside advisors from the scientific and global health community. The PPB Executive Committee, in consultation with a review panel of independent, external experts, will oversee the review and selection of specific projects from among the solicited proposals to insure that funded proposals are consistent with the overall objectives of the PPB. In collaboration with research investigators, the Executive Committee will also , develop key indicators of success and critical milestones for each project, as described in Section 4.2.

Assuming proposals of sufficient scientific merit, the level of funding requested should be commensurate with the type and scope of the research proposed to assure completion of the goals in the initiative time frame. This competition is expected to fund 6-10 grants. It is anticipated that, depending upon the scope of work proposed, the total budget for each project including institutional, indirect costs, will not exceed \$2,000,000 US dollars for the entire three to four year funding period.

### 5.2 Application Instructions & Review Process

This RFP will utilize an online application process:

#### Step 1:

Complete the online form at [www.gapps.org/healthybirth](http://www.gapps.org/healthybirth)

**Step 2:**

Submission of a Letter of Inquiry (LOI) to GAPPs by January 31<sup>st</sup>, 2012. There is a five (5) page limit on the LOI, with a general questions face page that does not count against the page limit.

Instructions for the completion of the LOI may be found at [www.gapps.org/healthybirth](http://www.gapps.org/healthybirth).

Applicant organizations submitting an LOI must fully meet the eligibility criteria listed on page 11 of this RFP. Elements included in the LOI must include:

1. Project background and rationale
2. Project objectives
3. General Approach
4. Anticipated outcomes and translational opportunities
5. Investigator and organizational capacity
6. Environment and resources
7. Estimated budget
8. Certification

Letters of Inquiry must be submitted electronically, using the forms, instructions, and process described at: [www.gapps.org/healthybirth](http://www.gapps.org/healthybirth). Each LOI must include in the header of the narrative pages the name of the investigator. Multiple LOIs from the same institution or organization are permitted. Those applicants who are eligible and have projects of further interest will be contacted directly and will be invited to submit a full proposal. GAPPs will not provide individual critiques of LOIs not selected to submit full proposals.

*Even at the LOI step, however, it is important to read carefully the full guidelines for applicants given below to make certain that the applicant organization is fully capable of complying with all the requirements and terms of award.*

**Submission of Full Proposal:**

If the LOI is successful, the applicant will be invited to submit a full proposal, not to exceed 20 pages. Instructions on the preparation of full proposals will be provided to selected applicants. Final selection will be based upon an evaluation of:

- Scientific and technical excellence
- Execution plan
- Translational potential for high-burden settings in the developing world.

The **evaluation criteria** that will be used to make a final selection of proposals for funding are as follows:

**Significance.** Is the approach likely to add dramatically to knowledge about the causative mechanisms and the development of potential interventions for preterm birth and stillbirth related to preterm delivery? Do the assays, technologies, and systems for analysis proposed have broad applicability?

**Approach.** Are the conceptual framework, design, methods, and analyses innovative, adequately developed, and appropriate to the aims of the proposal? Does the proposal acknowledge potential problem areas and consider alternative tactics? Is the likelihood of successful project completion high within the funding period? Are the proposed timelines and interim milestones appropriate, feasible, and technically sound?

**Organizational and Investigator Capability.** Is the research and development team appropriately trained, experienced, and positioned to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other proposed researchers? Is there strong evidence of substantive organizational capability and commitment? Is there experience in development of partnerships, multi-investigator project experience? Are collaborative arrangements in place? Is there evidence of an infrastructure for adoption of standard operating procedures, data collection, transfer, and sharing?

**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?

**Translational Feasibility.** Is there potential for advancing scientific findings into pre-clinical development? Is there reasonable gain in knowledge at a reasonable cost?

Additional review criterion: In addition to the above criteria, proposals will also be reviewed regarding protection of animals and human subjects and/or data and specimens, to minimize any adverse effect of the project proposed in the application.

### 5.2.1 Application Schedule

Letters of Inquiry must be received by January 31<sup>st</sup>, 2012, as summarized in Table 1. Full proposals from invited applications will be due on May 1<sup>st</sup>, 2012. Final awards are anticipated in July, 2012. The following schedule lists important deadlines and is subject to change:

<i>Process</i>	<i>Date</i>
Release of RFP and request for LOIs	11/07/2011
Letter of Inquiry Due	01/31/2012
Requests for full applications for selected LOIs	03/15/2012
Full Application Due	05/15/2012
Awards distributed	07/14/2012

### 5.2.2 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 respective topic areas. Grantees awarded projects will be required to actively collaborate with members of this research consortium.

### 5.2.3 Allowable Costs

Grant funds may be used for the following costs: personnel, necessary travel, supplies, contracted services, sub-grants, and consultants. Partial or full support for equipment may be requested subject to the circumstances described below. Please provide budget estimates according to these categories.

- Equipment: 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 GAPPS 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: GAPPS provides a limited amount of indirect costs, if any, based on the nature of the applicant organization. Indirect costs must be included within the total budget.

### 5.2.4 Privacy Notice

To help the governing Executive Committee and GAPPS staff in their evaluation and analysis of projects, all proposals, documents, communications, and associated materials submitted to GAPPS (collectively, “Submission Materials”) will become the property of GAPPS and may be subject to confidential, external review by independent subject matter experts and potential co-funders in addition to analysis by GAPPS and the foundation. Please carefully consider the information included in the Submission Materials. If you have any doubts about disclosure of confidential or proprietary information, GAPPS 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, GAPPS and the 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.

### 5.2.5 Warranty

By providing any Submission Materials, the sender warrants GAPPS, Seattle Children’s, and 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 GAPPS at [gappsgrants@seattlechildrens.org](mailto:gappsgrants@seattlechildrens.org)

### 5.2.6 Intellectual Property

Since the output of this program may lead to innovative technologies and/or products for use in the developing world, the successful development of these products may require involvement and support of the private sector, and may also involve collaborations with multiple organizations, including academic and/or non-profit research institutions. Intellectual property rights and the management of intellectual property rights may play an important role in achieving the goals of this program. GAPPS' Global Access Strategy will guide our approach to intellectual property, and we urge all applicants, even at the Letter of Inquiry stage, to consider their willingness to submit a full proposal in compliance with the GAPPS Global Access Strategy, the guiding principles of which are as follows:

- Appropriate solutions to global health challenges are made accessible to people most in need, particularly in the developing world. Accessibility relates to price, supply, and availability.
- Knowledge gained through discovery is broadly, and as promptly as possible, distributed to the global scientific community.

Grantees will be required to develop and sign a Global Access Agreement with GAPPS in line with the guiding principles. For further information, please refer to GAPPS' intellectual property policy at [www.gapps.org/healthybirth](http://www.gapps.org/healthybirth).

### 5.2.7 Additional administrative requirements

While this document provides an overview of the Preventing Preterm Birth initiative rules and regulations, additional requirements may be added at the time that full proposals are requested from eligible investigators.

## 6 RESEARCH ASSURANCES

While not necessary for the LOI, as applicable to the individual project, GAPPS will require that for each venue in which any part of the project is conducted (either by your organization or a sub-grantee or subcontractor) all legal and regulatory approvals for the activities being conducted will be obtained in advance of commencing the regulated activity. GAPPS will further require you to agree that no funds will be expended to enroll human subjects, nor engage in animal studies, until the necessary regulatory and ethical bodies' approvals are obtained.

### 6.1 Research Involving Human Subjects.

Research supported by this award must comply with the International Conference on Harmonization (ICH) guidelines. 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 and submitted to GAPPS for review.

### 6.2 Clinical Trials

We do not expect any projects in this research program to conduct clinical trials.

### **6.3 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.

### **6.4 Regulated Activities**

The coverage requirements set forth in the preceding paragraph include but are not limited to regulations relating to: research involving human subjects; 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.

### **6.5 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 GAPPs if the facts and circumstances change regarding the approval status of the IRBs or ethical committees for any final protocol(s).

### **6.6 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 be similarly developed, approved and implemented with notice to the employees.

### **6.7 Use of Animals in Research**

You agree to be responsible for the humane care and treatment of animals in projects supported in part or entirety by GAPPs 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 GAPPS. 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](http://www.cioms.ch/publications/guidelines/1985_texts_of_guidelines.htm)) if there is not a relevant national standard.