Family Health

Grand Challenges in Global Health

# Preventing Preterm Birth Initiative

## Enhancing Research Sites in High-Burden Countries for Studies of Pregnancy and Preterm Birth

**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 identify and develop research sites in low- and middle-income countries as part of a collaborative, multicenter initiative to conduct prospective studies of pregnant women that will investigate causes of preterm birth and stillbirth and novel strategies for prevention.

**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. The field of preterm research, particularly in high-burden, low-resource countries, has been constrained by the general lack of collaborative, multi-center, well-characterized pregnancy cohorts with sufficient sample size and standardized systems for data and specimen collection to investigate the complex and multiple causes of preterm birth. As a consequence, there are few broadly-applicable, preventive and therapeutic interventions to prevent preterm birth and stillbirth.

Globally, an estimated 15 million infants are born preterm each year. More than one million infants die due to complications of preterm birth, making complications of preterm birth the most frequent cause of all under-5 child deaths worldwide.[1] More than 40% of all under-5 child deaths occur in the neonatal period (within the first month of life), and preterm birth is the leading cause of all neonatal deaths. The situation is especially dire in low- and middle-income countries where 98% of all neonatal deaths occur each year.[2] Sub-Saharan Africa and South Asia in particular have the highest maternal, fetal, and neonatal mortality rates and the lowest rates of hospital deliveries and access to newborn care. In these regions, access to life-saving interventions for mothers and infants are often extremely limited. As programs move forward to improve maternal and neonatal care, so must an expanded research agenda to identify novel strategies for prevention.

There is an urgent need for the formation of a network of research sites to advance 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 prospective cohort studies must be large and must carefully characterize pregnancy and birth outcomes, and be linked to novel etiologic research to investigate the complex processes that result in adverse maternal, fetal, and neonatal health outcomes, especially in the context of populations most affected.

[1] Liu L, Johnson HL, Cousens S, et al., for the Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 2012;379:2151-61.

[2] March of Dimes, PMNCH, Save the Children, WHO. Born Too Soon: The Global Action Report on Preterm Birth. Howson CP, Kinney MV, Lawn JE, eds. Geneva: World Health Organization, 2012.

# 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 a decade ago. Research infrastructure to advance scientific knowledge of pregnancy and perinatal health remains globally under-resourced, leading to inadequate effort being applied to understand normal pregnancy, its perturbations, and innovative targets for prevention that are particularly relevant to low- and middle-income settings.

**Request for Proposals**

***The present Request for Proposals (RFP) is the second call for proposals of the Preventing Preterm Birth initiative*.** The objective of this RFP is to identify global health research sites to serve as part of a network to conduct well-characterized, standardized, prospective studies of pregnant women, in partnership with other investigators of the PPB initiative. It is intended that these multi-center investigations will collect information that will allow detailed investigations of the multiple and complex causes of preterm birth in an effort to identify innovative strategies for preterm prevention in low- and middle-income countries. While preterm birth and stillbirth are but a few of a number of adverse pregnancy outcomes, their primary importance is reinforced by: (1) the lack of existing, widely applicable, preventive solutions, (2) the broad applicability and particular relevance to low- and middle-income country 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.

**Primary Goals**

The overall goal of the Preventing Preterm Birth initiative is to support a broad plan to bring new investigators, novel technologies, and global research capacity to the field of maternal, neonatal, and child health. The specific objective of this second release for the PPB is to establish a collaborative network of research sites from low- and middle-income countries to conduct prospective studies of pregnant women. While advancing research of individual investigators and institutions, we expect the network to build an open and broad-based sharing of specimens, research approaches, protocols, and data essential to discovery studies. The primary goals are to:

1. Develop sites for global health research to investigate underlying mechanisms leading to preterm birth, or stillbirth associated with preterm birth, in high-burden cohorts.
2. Identify research sites in low- and middle-income countries to conduct prospective studies of pregnant women, in collaboration with other investigators funded by the PPB initiative. The sites selected in this RFP must have existing cohorts of pregnant women in high burden low resource settings, with the capacity to enroll and follow pregnant women through pregnancy and delivery; collect, process, and store appropriate biologic specimens; and collect and manage patient information. Support for clinical trials, per se, will not be provided in the context of this RFP.

Studies funded through this initiative are intended specifically to be part of a PPB network that conducts prospective studies of pregnant women to validate gestational origins, biological mechanisms and immunological responses to infection, inflammation, and nutritional conditions that lead to preterm birth and stillbirth. ***The goal of this RFP is to identify existing research sites in low- and middle-income countries to conduct investigations of preterm birth and serve as collaborating centers in scientific studies to advance the understanding of the causes of preterm birth and stillbirth and identify novel strategies for prevention relevant to low-resource settings.***

**Note:**
Information on the first awards of the Preventing Preterm Birth initiative can be found at: www.gapps.org/healthybirth.

# 3 PROJECT OBJECTIVES:

The limited research infrastructure in low- and middle-income countries for prospective studies of pregnancy health has been a major limiting factor for discovery science needed to advance the understanding of the complex causes of preterm birth and stillbirth, and identify new opportunities for prevention. Emerging science is building a solid case linking maternal infection, nutrition, and inflammation as primary drivers of preterm birth and stillbirth. 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, which risk populations to target with any new or existing interventions, and the critical timing during gestation and fetal development for targeting any particular intervention. At the root of these issues is the need for capacity in resource-restricted settings to investigate the mechanistic basis (e.g., the molecular pathways and physiologic changes) that mediate preterm birth and stillbirth in the context of infectious disease, inflammatory response, and nutritional deficiency, and to validate these findings in context-specific settings.

**Characteristics of successful proposals**

The goal of this RFP is to identify research sites in low- and middle-income countries with the capacity to conduct prospective studies of pregnant women that will eventually lead to or refine preventive interventions for preterm birth or stillbirth related to preterm birth.

Successful proposals should include documentation of the research site's demonstrated capacity to conduct prospective studies of pregnant women and investigate birth outcomes. The site must have the capacity to enroll women early in pregnancy, preferably in the first trimester or soon thereafter, and implement systems for accurate determination of gestational age using ultrasound and/or other precise methods for determination of gestational age. In addition, the site must demonstrate capacity to follow women during pregnancy; assess medical and other complications of pregnancy; collect blood, urine, and vaginal swabs during pregnancy; and characterize specific birth outcomes, including stillbirth and specific preterm phenotypes (e.g. preterm premature rupture of membranes, small for gestational age, medically-indicated preterm birth, and spontaneous preterm birth). Ability to access a large proportion

of enrolled women at the time of delivery will also be important, in order to collect critical information on maternal and infant birth outcomes, maternal and cord blood, and placentas. Sites must also demonstrate a documented capacity for the collection, transport, processing, and storage of specimens, as well as laboratory capacity for some clinical diagnostics.

Investigators managing existing cohorts or other research studies involving pregnant women are encouraged to apply, including those that do not currently study preterm birth. Collaborating institutions, cohorts, or hospitals may apply under one application. Investigators of PPB field sites will be linked with those of other preterm birth researchers funded through the PPB initiative. The intended outcome is to conduct investigations to identify practical, affordable, and scalable interventions to prevent preterm birth and preterm-related stillbirth. The studies conducted in human cohorts funded by this RFP will provide research opportunities for PPB-funded investigators, and are expected to be conducted in a collaborative fashion with other PPB cohorts. The PPB-funded studies were identified to investigate the causes, pathways, and mechanisms of preterm birth that are directed towards prevention of disease. The research infrastructure of applications sought in this current RFP will be used to address specific hypotheses from PPB-funded studies, inform pre-clinical development strategies, and ultimately focus and support the design of intervention trials among pregnant women in low resource settings.

**Successful proposals should include information on the documented capacity of the research site to accomplish the following:**

1. Enroll large numbers of women early in pregnancy, preferably in the first trimester. Preference will be given to sites that can enroll a minimum of 3,000 women per year in order to achieve sufficient sample size to conduct nested case-control investigations of preterm deliveries. Collaborating sites may apply under one application.
2. Perform ultrasound and/or other precise methods for determination of gestational age early in pregnancy, or have the capacity to implement such systems if provided with sufficient training and oversight by PPB collaborators.
3. Achieve high follow-up rates, and complete follow-up visits of pregnant women at least once during pregnancy after the time of enrollment and prior to delivery.
4. Collect blood, vaginal swabs, urine, and data at enrollment and at follow-up visits.
5. Availability of trained staff with the capacity to accurately assess and document medical complications of pregnancy, labor, and delivery.
6. Have methods to collect data and specimens, including placentas, from a high proportion of enrolled women at the time of delivery, with potential strategies to increase hospital deliveries.
7. Have the capacity to collect, transport, process, and store biological specimens using standardized protocols.
8. Have existing prospective studies of pregnant women or other population-based cohorts in low- and middle-income countries, with the ability to follow commonly-adopted standard operating procedures for prospective collection of data and specimens. Current studies should be related to investigations of pregnancy and adverse pregnancy outcomes, and do not need to be investigations of preterm birth *per se*, but should have the ability to build in

investigations needed for prospective studies of preterm birth and other adverse pregnancy outcomes.

9. Have the interest and ability to conduct collaborative research as part of a consortium, which will advance the research of individual investigators as well as strengthening opportunities of the group. Any research consortium agreements with investigators will be negotiated as part of the grant itself; specifics regarding data sharing and collaboration will be a component of the full proposal application. Data sharing should comply with established formats and protocols.

**Proposals that will not be considered for funding:**

We will not consider proposals from sites that do not have demonstrated experience in enrolling and following large numbers of pregnant women in low-income settings or proposals that fail to demonstrate willingness and ability to participate in sharing results, data, and other forms of collaboration with other PPB investigators.

# 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 conduct large prospective studies of pregnant women to investigate hypotheses using state-of-the-art systems. Collaboration and cooperation among research investigators will be established in an effort to conduct cross-disciplinary studies that could provide the most detailed investigation of hypotheses, validation, and interventions appropriate to low-resource settings.

## 4.2 Program Activities

Investigators will outline specific activities and milestones related to cohort enrollment and follow-up as a method to track project performance. 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 periodically 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 the time of the initial award;
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 outcomes towards a translatable discovery;
5. Continued alignment of each project with the program objectives;

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 the PPB initiative is to create a network of individually-funded projects and human cohorts that will benefit from collaboration, standardization of case definitions and data collections, as well as information sharing activities among its members. The collaborative nature of implementing standardized methods for patient enrollment, case definitions, specimen collection, and data across sites is intended to link innovative preterm researchers with strong, harmonized field activities to achieve well-characterized studies of pregnant women with the combined sample size required to investigate the multiple causes of preterm birth. This collaborative approach is intended to increase the efficiency of the overall effort to discover novel interventions for those most in need in low- and middle-income countries. 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 establishing 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 Gates 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, efficient, and protects the intellectual property of participating investigators, which will include:
    a. a data sharing and publication policy
    b. data use agreement
    c. PPB manuscript citation
    d. acknowledgement or coauthorship with the core PPB investigators.

# 5 RULES AND GUIDELINES

## 5.1 Program Direction

An Executive Committee will provide oversight of program management, with representation from GAPPS, the Bill & Melinda Gates Foundation, and two to 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 are of sufficient 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 an additional 3-5 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 $1,300,000 US dollars for the entire three year funding period.

## 5.2 Application Instructions & Review Process

This RFP will utilize an electronic application process:

**Step 1:**

Download the application and instructions at www.gapps.org/healthybirth

**Step 2:**

Submission of a Letter of Inquiry (LOI) to GAPPS by January 15, 2013. LOIs should be 3-4 pages in length (four page limit), which includes a general questions face page. Instructions for the completion of the LOI may be found at www.gapps.org/healthybirth.

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

1. Project background and rationale
2. Project objectives
3. General approach
4. Anticipated outcomes should include: number of women enrolled, gestational age at enrollment, accurate gestational age determination, follow-up rates, ability to characterize medical complications of pregnancy and preterm birth phenotypes, and anticipated number and proportion of deliveries for which data and specimens could be collected.
5. Investigator and organizational capacity
6. Environment and resources
7. Estimated budget

Letters of Inquiry must be submitted electronically, using the forms, instructions, and process described at: www.gapps.org/healthybirth. Each LOI must include the name of the investigator in the header of the narrative pages. Multiple LOIs from the same institution or organization are permitted. More than one institution or organization may submit a collaborative project under one LOI. 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, 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 12 pages. Instructions on the preparation of full proposals will be provided to selected applicants. Final selection will be based upon an evaluation of:

- Documented capacity of the site to enroll women early in pregnancy, accurately determine gestational age, achieve high follow-up rates, document medical complications of pregnancy, and provide accurate determination of stillbirth and preterm phenotype.
- Execution plan

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

**Approach:** Are the design and methods sufficiently rigorous to ensure accurate gestational age dating, standardized methods for collection of data and specimens, have sufficient clinical capacity to accurately document complications of pregnancy and birth outcomes, and effectively collect and store blood, urine, vaginal swabs, and placentas for later laboratory investigation? Does the proposal include community participation, communication, and if indicated, incentives or transport options to ensure sufficient sample size and, if indicated, hospital deliveries? If the proposed study of pregnant women is being added to existing intervention trials among pregnant women, can the analysis plan sufficiently control for differences in treatments between study groups? Does the proposal acknowledge potential problem areas and consider alternative tactics? Is there a strong likelihood of successful project completion within the funding period? Are the proposed timelines and interim milestones appropriate, feasible, and technically sound?

**Organizational and Investigator Capability:** Is the research team appropriately trained, experienced, and positioned to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator, other researchers, and field staff? Is there strong evidence of substantive organizational capability and commitment? Is there experience in development of partnerships with communities, participating hospitals, and host governments to achieve project results? Are country partners and other collaborative arrangements in place? Is there evidence of an infrastructure for adoption of standardized procedures for data and specimen collection, transfer, and sharing?

**Environment:** Does the environment in which the work will be done contribute to the probability of success? Does the site have demonstrated capacity for collection, transport, storage, and testing of biological specimens? Does the laboratory have documented capacity for accurate specimen management? Does the proposed cohort take advantage of unique features of the scientific environments, including partnerships with communities, hospitals, local universities, and governments for collaborative arrangements? Is there adequate evidence of institutional and host government support? Is the host government willing to invite outside collaboration with preterm investigators as

research partners, including use of specimens for laboratory investigations conducted outside the host country?

**Additional review criterion:** In addition to the above criteria, proposals will also be reviewed regarding protection of human subjects, 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 15th, 2013**, as summarized in Table 1. Full proposals from invited applications will be due on March 7th, 2013. Final awards are anticipated in May, 2013. The following schedule lists important deadlines and is subject to change:

| *Process* | *Date* |
|---|---|
| Release of RFP and request for LOIs | 12/11/2012 |
| Letter of Inquiry Due | 01/15/2013 |
| Requests for full applications for selected LOIs | 03/29/2013 |
| Full Application Due | 04/29/2013 |
| Awards distributed | 07/01/2013 |

### 5.2.2 Eligibility Criteria

Applicant organizations may be individual non-profit organizations, for-profit companies, universities, 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 the PPB 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.

### 5.2.6 Intellectual Property

Since the output of this program may lead to innovative technologies and/or products for use in low- and middle-income countries, 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 and host governments. 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 low- and middle-income countries. Accessibility relates to price, supply, feasibility, 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 the GAPPS intellectual property policy at 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 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 PPB projects to conduct clinical trials; however, these prospective investigations of pregnant women may be added on to existing, approved clinical trials.

## 6.3 Coverage for all Sites

Investigators must 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. Further, investigators 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

All investigators 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 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.