

Memorandum of Agreement between collaborating investigators in Preterm Birth Genome Project (PGP)

I. Goals of the PGP consortium

The goal of this collaboration is to identify genes that affect susceptibility to preterm birth (PTB) and other adverse pregnancy outcomes associated with preterm birth. This objective will be expedited by combining the resources of multiple research groups from around the world. This venture represents a new approach to the study of the genetics of PTB, and is intended to provide adequate research resources that will enable the discovery of important genes that would otherwise be difficult, if not impossible. The PGP will be used to: 1) organize and perform a Genome-wide association (GWA) study of PTB in multiple populations; 2) replicate findings from the GWA and genes found in prior studies.

This document sets out the collaborative agreements of the PGP consortium.

II. Background

The Preterm Birth International collaborative (PREBIC) was formed in 2003 to identify and study risk factors for PTB and to promote the biological understanding in human and animal model systems. In 2004, a second group that formed out of PREBIC, Preterm Birth Genetics International Alliance (PREGENIA), was formed to specifically investigate genetic risk factors. Since the formation of these two groups the technology to investigate the genetics of complex disease has progressed to the stage where GWA is now feasible for virtually any phenotype. In April, 2007 the PREBIC genetics group proposed the formation of a consortium of investigators to pursue GWA studies by combining samples from multiple investigators to adequately power the studies and to replicate results. Based on this proposal PREBIC leadership has solicited information regarding existing and soon to exist resources. This document and the PGP is an outcome of this effort.

III. Research Objectives

The objective of the PGP is to perform GWA in samples from multiple populations. Samples of the same ancestry will be combined for GWA, and replication samples will be generated from each population. Results will be compared across populations.

IV. Guiding Principles

The collaboration is based on shared objectives and consensus about the best way to identify PTB susceptibility genes. These are outlined below:

1. Trust

This memorandum of agreement must be based on mutual trust and respect among the participating groups. Without trust and respect this collaboration will not be possible. Members may disagree with each other but that cannot erode the fundamental sense of trust and respect. Participation in the collaboration is contingent on each group affirming these fundamental bases at all times.

2. Confidentiality

Findings and results generated by the PGP will be treated as confidential, but can be used with prior consent of the consortium for grant applications and presentations. Use of data after the primary publication will be governed by the principles outlined below. All scientists involved in the collaboration will declare possible conflicts of interest and will sign a document promising confidentiality.

3. Open Communication among senior investigators

For this collaboration to succeed all decisions and activities must be conducted in an open way. Specifically, decisions must be conducted in a transparent manner. This is best accomplished through clear, frequent and open communication among all the participating groups, either by phone, by email or through the virtual private network. Each senior investigator is responsible for forwarding all communications to members of their own group. A LISTSERV will be established to expedite communication.

4. Timeliness of activities/research

There is a commitment to adhere to reasonable timelines in sending the clinical and demographic data to the common data set, in reviewing analytic plans, carrying out analyses and publishing papers.

5. Shared consensus on the need for a PGP Management Committee

The collaboration needs a strong committee to run the everyday tasks of the project. However, the collaboration can only be successful if it also makes maximum use of the creativity and energy of the participating research teams. Thus, the Management Committee will not dictate plans for analysis or authorship. Rather, these will emerge from the Scientific Committee as outlined below.

6. A commitment to respecting priority.

If one of the PGP collaborating groups has positive results, using only samples that they collected themselves, it is understood that they may publish that finding before any other member of the collaboration can follow it up in a publication. If however, the finding involves samples *other than their own*, this does **not** apply. If this work has been supported by the Consortium, the Consortium should be recognized in the publication.

7. All parties to the collaboration benefit.

The first and foremost objective of the PGP consortium will be finding the genes that confer susceptibility to PTB, leading to a better understanding of the causes of PTB and development of potential treatments. The investigators may also benefit through increased or stable funding, further learning opportunities, the potential for career advancement, and learning more about the most appropriate strategies to uncover the genetic mechanisms of complex disease. The investigators and funding agencies may also benefit from owning intellectual property from any discoveries that are made. There is a clear recognition that for this collaboration to go ahead, any decisions that are made must attempt to provide mutual benefit for all those involved in the PGP. It will be difficult to ensure that the benefit is equally distributed, or that it is equal in kind among all partners; nevertheless there must be an assurance of mutual benefit.

8.

V. Administrative structure The consortium will be overseen by a Director who will interact with all committee structures to ensure smooth operation of the consortium. This individual will not be from one of the centers providing samples and will represent a balanced point of view.

1. Management Committee

- a. Membership: The Management Committee will consist of 7 voting members chosen from the PGP and PREBIC. A WHO representative will serve as Chair of the Management Committee, but will not have voting rights on the committee. The Management Committee will either perform the following specific tasks or delegate them to members of the consortium. Each contributing site will designate a liaison to the Management Committee.
- b. Responsibilities
 - i. The Management Committee will decide issues of committee membership
 - ii. Oversight of logistics
 1. Administrative support
 2. Meeting arrangements
 3. Communication among PGP members and committees
 - iii. Consortium agreements
 - iv. Informed Consent and IRB issues - A standing subcommittee will be appointed by the Management Committee to draft protocols and guidelines.
 - v. Intellectual property
 - vi. Financial matters, independent of specific grant mechanisms
 1. Soliciting private support for the research
 2. Managing consortium operational expenses
 - vii. Authorship – A standing subcommittee appointed by the Management Committee will decide upon publication priorities and timing. This subcommittee will in consultation with the Management committee set authorship guidelines, including author inclusion and roles in publication.
 - viii. Sharing of data after primary publication and with those outside of consortium
 - ix. Inclusion in PGP, based on recommendations from Scientific committee
- c. Decision Making Process – Decisions of the Management Committee will be based on majority votes. A quorum consists of 5 voting members.
- d. Appointment to the Management Committee - The Management Committee will be elected by the entire consortium. Each contributing site will get one vote. In order to achieve continuity four members will be elected for a term of four years. Three members will serve an initial term of three years, and these positions will revert to four year terms after the initial three years are served. Each contributing group will be eligible to nominate up to two names.

2. Scientific Committee

- a. Membership: The Scientific Committee will consist of representatives from the contributing research groups (those contributing samples and/or other scientific resources to the project). Each contributing research group will have the option of having one representative serve on at least one Scientific subcommittee. An Executive Committee of the Scientific committee will include five members. One member will serve as Chair of the Scientific committee and will not be a voting member. This member will not chair any of the subcommittees of the scientific committee. The chairs of the subcommittees will also serve on the Executive Committee of the Scientific committee with the Chair.
- b. Responsibilities: The Scientific committee will be responsible for directing the scientific activities of the PGP, including grant preparation, sample selection/phenotypic criteria, genotyping, analyses, and manuscript preparation.
- c. Subcommittees
 - i. Sample selection – will set standards for inclusion of samples including specific phenotypic criteria and quality and amount of DNA
 - ii. Genotyping – will oversee the arrangements of collection of genetic data and data quality control.
 - iii. Database management and data analysis – will oversee construction and maintenance of the PGP database, quality control of the database, and all association analyses
 - iv. Prospective collection and replication data set – will aid in the design of new studies to be included in the consortium and will work with researchers who intend to join the consortium.
- d. Decision Making Process – Decisions of the Scientific Executive Committee will be based on majority vote. In the case of a tie the Chair will serve as the deciding vote. Subcommittee decisions will be based on majority vote and a quorum will be 75% of subcommittee members. No individual may serve on more than two subcommittees.

3. Steering Committee

- a. Membership: At least one member from the Management and at least one member from the scientific committee will comprise the Steering committee. This should include the chair of each of the two committees. The Director will also serve on the steering committee. At least two additional members will be appointed who are not contributors of samples to the consortium.
- b. Responsibilities – The functions of the Steering Committee are 1) evaluate the program of the collaboration 2) to monitor progress of the PGP; 3) to monitor the effectiveness of communications within PGP 4) to advise on personnel and methodology changes; 5) to adjudicate disagreements 6) to keep the PGP in touch with perspectives of research efforts impacting on the PGP.
- c. Decision Making Process – A quorum consists of 75% of the steering committee. Decision will be made by majority vote.