GUIDELINES FOR INVESTIGATOR INITIATED STUDIES PROGRAM

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1 Change Log

Version N°	Description of change (including reason for change)	Date
1.0	New version	29-04-2016
2.0	Changed terminology of studies Updated evaluation criteria terminology Aligned terminology of Investigator/Sponsor Added Site & Investigator Evaluation Form requirements Clarified studies typically not supported Added recommendation of external monitoring for clinical studies Clarified that a site visit might be organized	25-10-2016
3.0	Clarified evaluation criteria and added availability of PMI Support	18-05-2017
4.0	Clarified that PMI support does not necessarily mean endorsement of all study design, methods, results or conclusions	23-10-2017
5.0	Reopening of IIS program	01-11-2021

2 Introduction

Philip Morris International (PMI) has dedicated significant resources to the development and assessment of Reduced Risk Products (RRPs)[1].

Since 2008, we have invested in fundamental research on tobacco related diseases, product development, methods to substantiate risk reduction and ways to assess RRP impact on population harm. We are continuing to share our scientific methods and data with regulators and the scientific and public health communities.
We are committed to transparent and independent advancement of RRP science and welcome scientists and institutions who have the relevant expertise to conduct such research. With this goal in mind, we have created the Investigator Initiated Studies Program (IIS).

An IIS is a third party research effort in which the Investigator (an individual or institution) designs and implements the study and acts as the study sponsor.
Acting as their own study Sponsor, the Investigator assumes all responsibilities for complying with applicable regulatory requirements.

An IIS may be supported in the form of material, technical and/or financial support through the IIS Program, as follows:

- Material support may include product(s) and/or equipment(s) necessary to conduct the study.
- Technical support may include technical know-how with regards to equipment and/or methodologies. Importantly, the technical support must only be provided to help cover the reasonable and justified needs of specified and documented research conducted pursuant to the study proposal. It must not be excessive or invasive, so as to jeopardize the independence of the investigator/sponsor.
- Financial support may include direct funds or external costs which are charged to PMI directly for the study.

We expect scientists and institutions whose proposals will be accepted to make their research available through appropriate and recognized peer-reviewed journals, conferences and repositories.

[1] *Reduced Risk Products ("RRPs") is the term we use to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continuing smoking. PMI has a range of RRPs in various stages of development, scientific assessment and commercialization. Our RRPs are smoke-free products that produce an aerosol that contains far lower quantities of harmful and potentially harmful constituents than found in cigarette smoke.*

3 Goal & Objectives

The goal of the IIS Program is to promote and support external studies that advance scientific/medical knowledge or verify PMI science for our developed and commercialized RRPs.

This global program is open to researchers and institutions who have the relevant expertise and scientific credentials to conduct the proposed study, complying with local regulations and who are interested in receiving support from PMI for conducting their own research.

Key objectives for this program are:

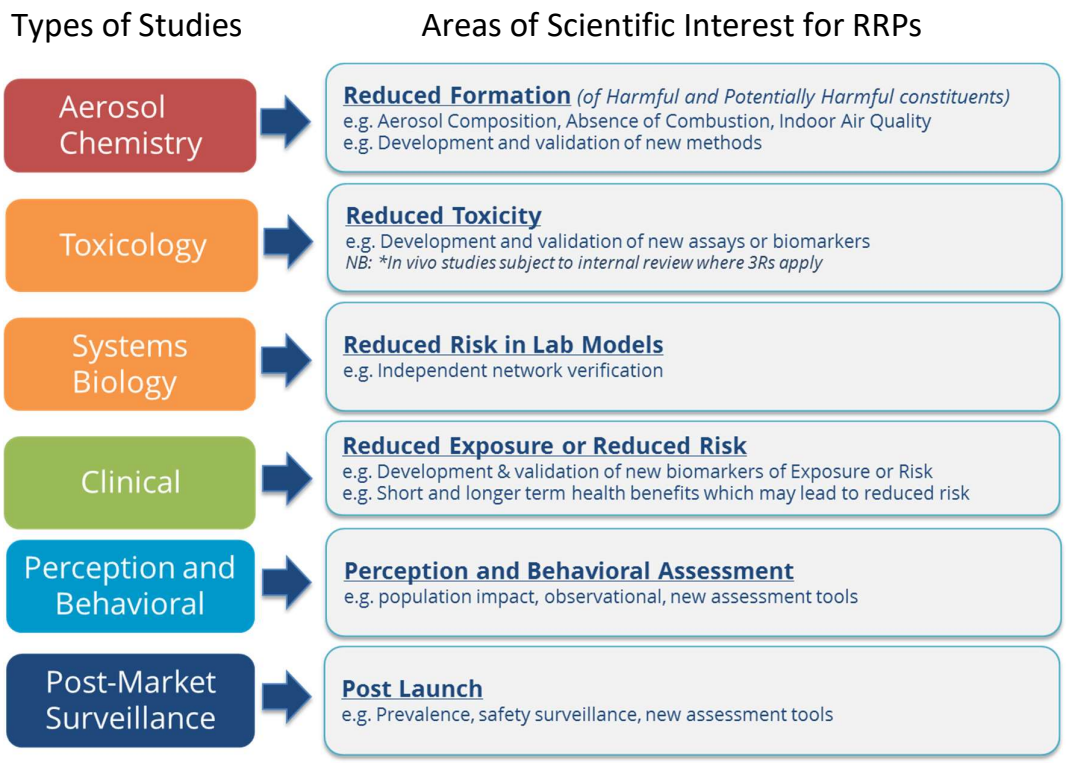
- To promote external studies about RRPs developed and commercialized by PMI
- To expand scientific/medical knowledge on RRPs
- To provide additional input that may broaden PMI's scientific perspective
- To provide a route to valuable studies that are not core to PMI's assessment program
- To facilitate the broadening of scientific publications related to PMI's approach/products

The evaluation and approval of an IIS is based on the following principles in no particular order:

- Maintaining scientific independence of the investigator from PMI
- Consistency of the IIS Proposal with the IIS Program scope
- Scientific strength (Degree of novelty & validation of RRP Science)
- Scientific credibility (Investigator's and institution's qualifications, expertise and track record)
- Scientific rigor (Study appropriately designed to test hypothesis with adequate sample size and methods)
- Scientific impact (Type of scientific study and value of the evidence)
- Scientific capability (Resources, facilities and partnerships)
- Compliance with regulatory framework & testing guidelines
- Quality standards (Certifications, validated methods/assays)
- Amount of Support requested (As a proportion of investigator contributed resources)
- Availability of PMI Support (Material, Financial, Technical)

4 Scope

This global program is open to researchers who are interested in receiving support for any type of studies listed below which advance scientific/medical knowledge or independently verify PMI's science on our developed and/or commercialized RRPs. Although verification of PMI's science is important, we typically do not find it ethically justifiable to replicate studies involving humans and animals, unless there is an exceptionally strong rationale.



**In vivo studies will require Animal Welfare Committee approval which applies the 3Rs (Replacement, Reduction and Refinement)*

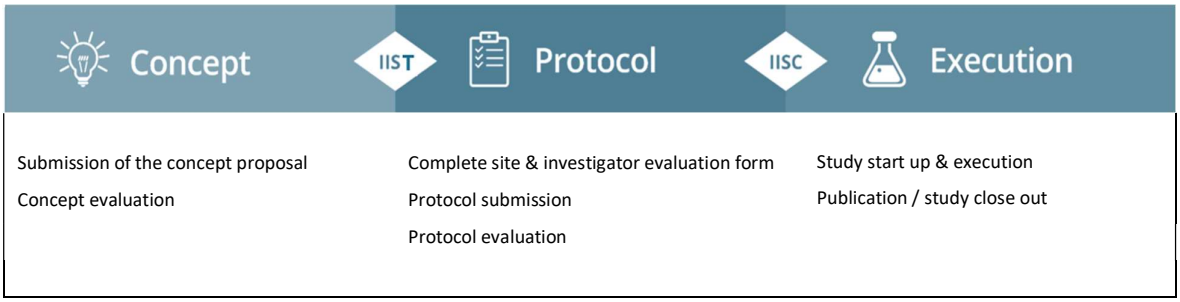
5 Pre-requisites

- Investigators and institutions must be recognized for their expertise and scientific credentials to conduct the proposed field of research with a proven track record in the subject matter of the proposal. Proof may be in the form of qualifications, publications, and certifications.
- Any misrepresentation of Investigator/Sponsor credentials will result in the immediate withdrawal of our support.
- Facilities/Labs/Sites follow appropriate recognized quality standards, e.g., ISO 17025, GLP, GCP OR at least:
  - Have a detailed study plan/protocol
  - Use robust and reproducible methods/assays
  - Have adequate facilities for study and demonstrate data integrity

6 Process

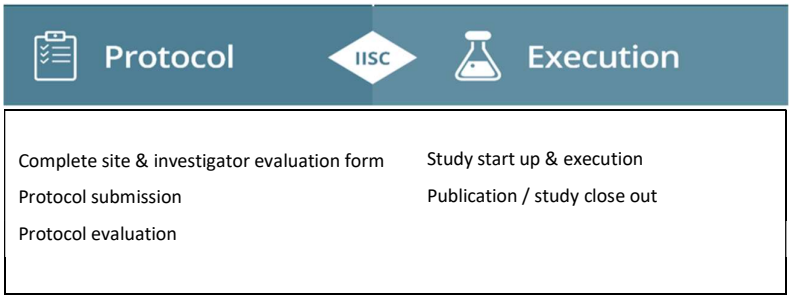
The IIS process comprises 3 main stages as indicated below: Concept, Protocol and Execution stages. The process follows distinct procedures for financial *versus* material/technical support (only).

Financial support:



IIST: IIS core team IISC: IIS steering committee

Material/technical support (only):



IISC: IIS steering committee

6.1 Concept Stage

6.1.1 Learn about PMI IIS Program

Program guidelines contain information to help understand:

- IIS Program and process
- Roles & responsibilities of the investigator

6.1.2 PMI IIS Website

- Read and accept Terms & Conditions
- Access Concept Proposal template

6.1.3 Submit Concept Proposal

- Submit Concept Proposal and additional information including CV and supporting documentation

A Concept Proposal must contain an adequate amount of information for PMI to determine interest in receiving a full proposal. The following information is mandatory:

General Information required	Scientific Information required
• Study Type • Investigator's contact information • Country of facility/lab/site • Type of support requested (if applicable) • Amount of direct fund requested (if applicable)	• Proposed Study Title • Reduced Risk Product Type • Background & Rationale • Scientific aim(s) & intended methodologies • Study Design and Study Duration

6.1.4 Concept Evaluation

- Concept Proposal to be evaluated by IIS core team.
- Decision relayed to proceed with Protocol stage or not (rationale will be provided)

The dimensions which the Concept Proposal will be evaluated against are:

- Scientific strength
- Scientific credibility
- Expected impact
- Compliance with local regulatory framework & testing guidelines
- Amount of Support requested
- Availability of PMI Support

If PMI has any questions or any matters to clarify at this stage, the PMI IIS Team will reach out to the Investigator/Sponsor. Based on the evaluation of the Concept Proposal, a site visit to evaluate the study site capabilities might be organized.

6.2 Protocol Stage

If the Concept Proposal is accepted by the IIS core team, a Site & Investigator Evaluation Form and Study Protocol template will be provided to the Investigator/Sponsor.

For technical/material support only, the level of information required below must be adapted to the level of support requested.

6.2.1 Complete Site & Investigator Evaluation Form

- Complete Site & Investigator Evaluation Form

- Prepare detailed Study Protocol

The Evaluation Form is to ascertain facility's/site's adequacy. The following information is requested:

- Name of investigator and institution/site that study will be conducted
- Site Quality and Compliance
- Site Supplier Management
- Site Study Capability & Capacity
- Site Documentation Standards
- Site Training
- Site Data Integrity
- Investigator/Sponsor Experience and Independence

6.2.2 Submit Study Protocol

- Submit detailed Study Protocol and additional information including total budget, timelines, milestones and deliverables.
- Budget and costs should be appropriately itemized and commensurate with fair market value

A detailed protocol submission must contain an adequate amount of information about the study for PMI to evaluate the proposal. The following information is mandatory:

General Information required	Scientific Information required
• Study Type • Reduced Risk Product Type • Investigator's contact information • Country of facility/lab/site • Resource requirements • Breakdown of study costs • Total study budget • Study duration, key milestones & deliverables	• Proposed Study Title • Background & Rationale • Scientific aim(s) & intended methodologies • Study Design • Study Procedures & Methods • Statistical Analysis Plan • Data Management Plan • Publication Strategy *

* How publications and data will be openly accessible and shared.

A budget with below-mentioned items requested (if applicable):

Direct Costs	Indirect Costs
• Study-related material costs • Study-related personnel costs • Diagnostic fees and services • Data management expenses • Subject-related costs (if applicable) • Animal-related costs (if applicable)	• Equipment/supply expenses • External services (e.g., labs) • IRB or ECA review fees • Publication costs • Data sharing costs

6.2.3 Protocol Evaluation

- Study Protocol to be evaluated by the IIS steering committee
- Decision relayed to proceed with Execution stage or not (rationale will be provided)

The dimensions with which the Study Protocol will be evaluated against are:

- Scientific rigor (design and methodology)
- Quality standards
- Scientific capability

6.3 Execution Stage

If the Study Protocol is accepted, an IIS contractual agreement will be provided.

6.3.1 Study Start Up & Execution

Before starting, the following is required:

- Signed IIS agreement
- Market authorization for product testing, if applicable
- Animal Welfare Committee (AWC, internal), Institutional Animal Care & Use Committee (IACUC) or other Oversight Bodies (OB) approval, if applicable
- Institutional Review Board or Ethics Committee approval, if applicable

During study execution, the following is required:

- Study is conducted according to the detailed Protocol and stated standards
- Periodic progress updates and safety reports (for clinical studies) to be provided by the Investigator/Sponsor throughout study according to the IIS agreement (depending on duration of study). For technical/material support only, the progress updates should remain limited.
- If an amendment or deviation of the study protocol is requested by the investigator, the IIS Committee will review the proposed change and make a decision as to whether to accept or reject the change. If research described in final study plan/Protocol is materially different from what is in the approved Proposal, then PMI reserves the right to reconsider its support.

6.3.2 Publication / Study Close Out

At the conclusion of the IIS, the Investigator/Sponsor shall provide the following deliverables in order to fulfill the IIS agreement requirements, as well as the open access and sharing of publications and data:

- Written status reports as well as final study closed out report, which summarizes deliverables as specified in the IIS agreement, will be completed and provided to the IIS program leader
- Scientific paper(s) to be published in open access peer-reviewed journals together with the corresponding Data Note, under a CC BY copyright license and in compliance with ICJME and GPP guidelines. For example, refer to the F1000Research guidelines as outlined here.
- For informational purposes only, appropriate publication details (name of the publication, date etc...) and a copy of the accepted publication should be provided within five (5) days following acceptance of publication by a journal.
- For a clinical study, the publication of a Study Protocol in a scientific journal as outlined here, published within three (3) months of the IIS program Protocol approval. Investigators may be invited to symposiums and conferences to showcase data and publications.

If the study is clinical in nature the investigator makes sure that the study (including results) is registered at www.clinicaltrials.gov as per the requirements of the registry.

7 Roles & Responsibilities of the investigator

Investigator/Sponsor will be required to acknowledge the Terms and Conditions which are found in a separate document. These are general for all types of studies and will be specified further in an IIS contractual agreement.

As the study Investigator/Sponsor, the researcher has responsibility for all aspects of the study, including, but not limited to:

- Initiate and conduct study from developing study Concept to publication
- Ensuring appropriate institutional, regulatory, and ethics committee compliance and approval
- Taking responsibility for ensuring appropriate adequate record keeping, medical monitoring, adverse event reporting and medical supervision
- Analysis, interpretation, and communication of the results (e.g., publications and submissions to conferences and journals)

It is recommended that Investigator/Sponsors arrange independent external monitoring of clinical studies.

Transparencies & Disclosures

- Investigator/Sponsor agrees to publicly disclose information as required by applicable laws, on conducting the IIS, type of support and the amount of funding provided, and expenses covered by PMI.
- Investigators must disclose PMI financial, scientific, technical and/or material support in any publications, presentations, and communications resulting from the study.
- The list of approved Protocols and type of support will be provided on the PMI Science website.
- Investigator/Sponsor agrees to register their IIS clinical study upon IIS program protocol approval (e.g. registration and results posting on www.clinicaltrials.gov).

8 Disclaimers

- All requests for funding are subject to a fair market value (FMV) analysis.
- Invitation to submit a full protocol or approval of funding of an IIS should not be interpreted that our RRPs are recommended for any use outside of market authorization.
- Submission of concept or protocol does not guarantee that it will be supported. The decision to support a research project will be evidenced by full execution of a research agreement.
- Proposals are evaluated on a case-by-case basis according to the criteria outlined in the section "Process" and we may not be able to support all requests received.
- Decisions regarding support for research are made at the sole discretion of PMI.
- All requests for funding are subject to Investigator/Sponsor agreeing that PMI may publicly disclose information about Investigator/Sponsor as required by applicable laws, including, but not limited to identifying Investigator/Sponsor as conducting the IIS, and the amount of funding provided, and expenses covered by PMI. PMI may publish this information on its website or make it accessible in various jurisdictions with different data protection laws that may not offer the same level of data protection as the country where the Investigator/Sponsor is based, or the IIS is to be performed.
- PMI support of an investigator-initiated study does not necessarily mean endorsement of all study design, methods, results or conclusion.