Data & Materials Sharing Agreement

Collaboration for AIDS Vaccine Discovery

Clinical Trials Data Sharing Addendum & Related Information

I. Overview of this Document

The primary purpose of this document is to provide background, clarifications, and proposed additions regarding clinical trials to the Data & Materials Sharing Agreement ("DMSA") for the Collaboration for AIDS Vaccine Discovery ("CAVD"). This document is also intended to explain how the CAVD DMSA and this Addendum, and the Bill & Melinda Gates Foundation (BMGF) Open Access Policy work together for CAVD Members.

Once agreement on data sharing among an initial group CAVD Members that are or soon will be involved in the conduct of clinical trials is reached, the proposed Clinical Trials Data Sharing Addendum (the "Addendum") will be signed by that initial group of CAVD Members, and will be subsequently signed by any additional CAVD Members that agree to be involved in CAVD-funded clinical trials.

II. Background and Purpose of the Addendum

The CAVD DMSA came into effect in 2006. At that time, the Bill & Melinda Gates Foundation (the "Foundation") was not funding CAVD Members to undertake clinical trials. Understandably, the DMSA did not include or exclude data sharing terms specific to clinical trials. Under the DMSA as it currently stands, CAVD Members are expected to utilize the services of the BMGF-funded Central Services Facilities (CSFs), which includes two Vaccine Immune Monitoring Consortia that provide standardized assays to characterize humoral and cellular immune responses. Data from these standardized assays are transferred to the Vaccine Immunology Statistical Center ("VISC"), shared with all CAVD Members and ultimately with the broader scientific community at specified times.

Though not currently an obligation on CAVD Members, results from assays not performed by the CSFs (but that are funded by the Foundation under a CAVD grant) should also be shared with CAVD Members. This encompasses immunological assays redundant with services available from the CSFs, as well as characterization by the clinical study team of participant specimens using other standardized, qualified or validated assays described in their study plan. Individual grant agreements may also require sharing of all data from assays performed on specimens from a foundation supported clinical study regardless of the source of the laboratory funding.

Prior to the initiation of any laboratory or statistical study by the Vaccine Immune Monitoring Centers ("VIMCs") or VISC, the Vaccine Development Consortium (VDC) will

work with the VIMC or VISC, as appropriate, to register the study on the CAVD portal. VDCs acknowledge the importance of consulting with the VISC regarding study design, data format, and data transfer methods, to ensure agreement of data definitions and plans for statistical analyses. Also since 2006, there have been new initiatives launched by the Foundation that change requirements and process for the sharing of data arising from foundation funding. In 2015 the BMGF launched an open access policy which includes a requirement to share the clinical trial data underlying peer-reviewed publications. What follows is background on the foundation's open access policy, and then details regarding the proposed Addendum to the CAVD DMSA that pertains specifically to the sharing of clinical trials data.

A. Open Access Policy

The Foundation's Open Access Policy[1] came into effect on January 1, 2015 and applies to all grants made after that date, including Foundation grants to CAVD Members.

The data sharing requirement of the Open Access Policy is in addition to the data sharing principles in the CAVD DMSA. Compliance with the data access requirements of the Open Access Policy can be achieved in several ways. One option for CAVD Members is to provide a link to the publication and underlying data and results to the CAVD Alliance Manager for posting on the CAVD's public web site. The linked data set would, of course, have to be open for others to download and use the data.

B. Sharing of Clinical Trial Data

The Addendum is intended to clarify and expand the data sharing to include clinical study data and results.

The Addendum and its provisions follow the results of a study conducted by the Institute of Medicine and released on January 15, 2015 entitled "Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk."[2]

Two overarching principles govern the construct and interpretation of the Addendum:

1. CAVD Members will not take any action in the gathering, dissemination or use of data that violates controlling law or regulations or generally accepted ethical standards for the conduct of clinical trials and sharing of resulting data; and
2. CAVD Members agree that rapid and broad sharing of clinical trial data can increase scientific knowledge and participation in the scientific processes to rapidly develop an AIDS vaccine.

[1] http://www.gatesfoundation.org/How-We-Work/General-Information/Open-Access-Policy
[2] http://www.iom.edu/activities/research/sharingclinicaltrialdata.aspx

These principles require CAVD Members to ensure that participants' consent is obtained and respected for data sharing activities, wherever possible, and that participant-level data is appropriately de-identified or anonymized to maintain confidentiality, in accordance with the Protocol and informed consent disclosure. It is also recognized that while the rapid and broad sharing of data is the ideal, CAVD Members that generate data may need to delay sharing data and results in the interest of protecting intellectual property rights that are important for the overall development program. But such delays will be limited to the time necessary to secure those rights. As described below in Section III.C.2, CAVD Members may select a site for the storage of the data sets governed by the Addendum.

III. Scope and Content of the Addendum

A. Results and Data Sets Governed by Addendum. The Addendum governs sharing of clinical trial results from Foundation funded research and of three categories of data sets:

1) **Summary Level Results.** The Bill & Melinda Gates Foundation strongly believes that outcomes (results) of clinical studies must be shared with the trial participants, community stakeholders, HIV-vaccine investigators and the public in a clear and timely way. Disclosure of the results of a trial include a description of the details of the study (including its purpose, location, products being tested, and study population), the outcomes of the study including adverse reactions and their frequency, and contact information for the sponsor of the study. A lay summary of trial results must be communicated in a manner that supports Good Participatory Practice for biomedical HIV prevention trials[3]. The disclosure of Summary Level Results and a lay summary thereof is not intended to include participant-level data.

2) **Full Data Set.** This includes the full analyzable data set (all participant-level data collected in the study, including safety, behavioral and immunogenicity data, and other sequencing and assay data pertinent to understanding the response of participants to the treatment under evaluation), the metadata about the study, metadata about the study product, and all versions of the protocol used in the trial, the full statistical analysis plan, data definitions, and analytic code. In other words, the data set should be deposited with sufficient detail and documentation such that the data can be understood and utilized. The full data

[3] http://www.avac.org/sites/default/files/resource-files/Good%20Participatory%20Practice%20guidelines_June_2011.pdf

set must be updated if new data from immunogenicity, virological, sequencing or other assays are performed on stored specimens and that work is funded by the Foundation or otherwise required to be shared in that individual grant agreement.

3) **Abbreviated Full Data Set**. For phase 1 and "Experimental Medicine" phase 1 studies, CAVD Members may provide a subset of the full data set. Experimental medicine studies are defined as those that are not intended to establish a substantial safety data base, or where the substances being tested are not intended to be developed into a drug or vaccine, or where the studies only enroll a very small number of participants to assess an important biomedical concept. For these phase 1 and experimental medicine phase 1 studies, an abbreviated version of the "full data set" containing study and product descriptors, demographic and baseline characteristics of participants and the key immunogenicity or assay data are acceptable. The following elements are those included in an "abbreviated full data set":
    a) **Study Metadata**. Study title, phase, milestones (start and completion dates), primary and secondary objectives, locations of participating sites, and treatment regimens (study products, treatment arms/groups, product administration and schedules for sample collection and study procedures.
    b) **Study product metadata**. Study product name, type (such as vaccine, biologic, or adjuvant), study product brief description, manufacturer and/or developer, and Investigational New Drug identifiers and holders.
    c) **Participant demographics and descriptors**. Subject characteristics (provided they are de-identified or anonymized), intervention days since enrollment (for example, treatment assignment, product administration visit days) and other data important participant data for the understanding of the study findings. For example, if anti-HIV products are given the HIV-infected subjects then baseline viral load and concomitant ARV medication data should be provided.
    d) **Assay data and metadata**. Assay data/values, assay name, type (such as cellular, humoral, or host genetic), a brief assay description (including method, platform, antigens, and analytes) and laboratory where performed.

B. Definition of Study Completion.

An important boundary to the above-described data sets is the definition of the study completion, which triggers the subsequent dates that the summary results and the full data set need to be released. CAVD Members must propose and the Foundation must approve the definition to be used to determine the study completion date, prior to the start of the study and as part of the data sharing plan, as well as providing that in the Study Protocol. A frequent definition for study completion is the date of the last participant's last study visit. Alternate definitions of study completion may be appropriate if the last participants last study visit definition is not supported by the study design.

C. Obligations Regarding Sharing of Clinical Trial Data

A data access plan, including at least the definition for study completion, will be established with respect to each CAVD grant from the Foundation, either in the form of a stand-alone document or as part of the grant agreement.

Clinical trials conducted by CAVD Members must be registered with the appropriate government agency and information about the trial should be made publicly available. The registration should occur prior to the start of the study. CAVD Members need to provide to the CAVD portal via the CAVD Alliance Manager the web site address with the appropriate accession number or web link to the registry. Examples: FDA's clinicaltrials.gov[4] or other agencies listed by the WHO's International Clinical Trials Registry Platform.[5]

Following study completion, CAVD Members must provide the following to the CAVD Alliance Manager for posting to the CAVD private or public web site.

1. **Summary Level Results.** Summary Level Results (including adverse event summaries) and a lay summary of the trial must be made available to the CAVD community no later than 6 months after study completion and publicly available no later than 12 months after study completion. To satisfy the requirement to share the Summary Level Results with the CAVD community the CAVD Member must provide the Summary Level Results to the CAVD Alliance Manager for posting to the CAVD Members-only portal, or provide a link as to where CAVD Members can access these materials. The CAVD Member may choose the mechanism by which the Summary Level Results and the lay summary thereof are made publicly available, if a link to where they are stored is provided to the CAVD Alliance Manager, for posting to the public

[4] http://www.clinicaltrials.gov/

[5] http://www.who.int/ictrp/en/

CAVD website. For example, CAVD Members may use existing services such as www.clinicaltrials.gov or publish the clinical trial results in an open access publication that includes a lay summary. See, for example, PLOS Pathogens Author Summary section and PNAS Significance Section). The Summary Level Results and the lay summary (as discussed in Section III.A.1.) do not need to be separate documents or postings if the CAVD Member can achieve the goal of clearly presenting results to a scientific and non-scientific audience with a single document or posting.

2. **Full or Abbreviated Full Data Set.** The clinical trial full data set (or abbreviated full data set) must be made available no later than 18 months following completion of the study so that other researchers can request access to the de-identified or anonymized participant level data. CAVD Members are responsible for ensuring that the selected site has submission and access policies in place, utilizes an independent peer review of requests, and provides controlled access following execution of a written data use agreement. Examples of clinical data sharing sites that have such policies include, but are not necessarily limited to, clinicalstudydatarrequest.com[6] and the Yoda Project[7]. The expense associated with sharing the full data set will be covered by the foundation if needed. The CAVD Member must inform the CAVD Alliance Manager where the data is located and the process by which the public can access the data so that this information can be provided on the CAVD public web site as per the DMSA.

3. **Post publication data**. For clinical trial data that is published, the post-publication data package must be shared. Sharing of the post-publication data package with information supporting the findings, tables and figures and figures of the publication will also fulfill the data sharing requirement of the Foundation's Open Access Policy.

[6] https://www.clinicalstudydatarequest.com/

[7] http://yoda.yale.edu/

CAVD DATA & MATERIALS SHARING AGREEMENT

Collaboration for AIDS Vaccine Discovery

Clinical Trials Addendum

THIS ADDENDUM is hereby entered into effective as of the date of signature on the signature page which follows.

WHEREAS, each Party is a member of the Collaboration for AIDS Vaccine Discovery (CAVD) and a signatory to the Data and Material Sharing Agreement (which entered into effect on December 11, 2006)

WHEREAS, the CAVD did not initially provide funds for the conduct of clinical trials;

WHEREAS, the Bill & Melinda Gates Foundation (the "Foundation") has decided to provide funding for the conduct of clinical trials and related activities as part of the CAVD; and

WHEREAS, the signatories to this Addendum (identified in Annex A) are recipients of funding from the Foundation to conduct clinical trials or related activities and have agreed to be bound by the terms of this Addendum.

Now, therefore, the Parties agree to the following terms and conditions:

1. The definitions, terms and conditions of the DMSA remain in full force and effect as among the CAVD Members, including the signatories to this Addendum. Hence, all capitalized terms not specifically defined in this Addendum will have the same meaning as given to those terms in the DMSA.

2. Section 1(a) ("Definitions") of Annex C (Data & Materials Sharing Guiding Principles) is amended by adding the following definitions:
    a. **"Full Data Set"** means the full analyzable data set (all participant-level data collected in the study, including safety, behavioral and immunogenicity data, and other sequencing and assay data pertinent to understanding the response of participants to the treatment under evaluation), the metadata about the study, metadata about the study product and all versions of the protocol, the full statistical analysis plan and analytic code. The full data set may be updated if new data from immunogenicity, virological, sequencing or other assays are performed on stored specimens from the Trial and that work is funded by the Foundation or otherwise required to be shared in that individual grant agreement.

b. **Abbreviated Full Data Set** means (as it relates to phase 1 and "Experimental Medicine" phase 1 studies) a subset of the full data set. Experimental medicine studies are those phase 1 studies that are not intended to establish a substantial safety data base, or where the substances being tested are not intended to be developed into a health-product and studies that only enroll a very small number of participants to assess an important immunogenicity concept. For these phase 1 and experimental medicine phase 1 studies, "abbreviated full datasets" containing study and product descriptors, demographic and baseline characteristics of participants and the key endpoint (e.g. immunogenicity or assay) data are acceptable. The following elements are included in an "abbreviated full data set":

    (1) **Study Metadata**. Study title, phase, milestones (start and completion dates), primary and secondary objectives, treatment regimens (study products, treatment arms/groups, product administration and sample collection schedules), and locations of participating sites.
    (2) **Study product metadata**. Study product name, type (such as vaccine, biologic, or adjuvant), study product brief description, manufacturer and/or developer, and Investigational New Drug identifiers and holders.
    (3) **Participant demographics and descriptors**. Subject characteristics (provided they are de-identified or anonymized), intervention days since enrollment (for example, treatment assignment, product administration visit days) and other data important participant data for the understanding of the study findings. For example, if anti-HIV products are given the HIV-infected subjects then baseline viral load and concomitant ARV medication data should be provided.
    (4) **Assay data and metadata**. Assay data/values, assay name, type (such as cellular, humoral, or host genetic), a brief assay description (including method, platform, antigens, and analytes) and laboratory where performed.

c. **"Post-Publication Data Package"** means a subset of the full data package supporting the findings, tables and figures of the publication.

d. **"Study Completion"** is the last study visit of the last participants' visit in the study unless the CAVD Member proposes an alternate definition of study completion before the start of the study in the Trial Protocol, and as part of the data sharing plan. Alternate definitions of study completion may be appropriate if the last participants last study visit definition if not supported by the study design. The

Foundation must approve any definition of study completion other than last study visit of the last participants' visit.

e. **"Summary Level Results"** include a description of the details of the study (including its purpose, location, products being tested, and study population), the outcomes of the study including adverse reactions and their frequency, and contact information for the sponsor of the study.

3. Section 1(e) ("Treatment of Data") of Annex C (Data & Materials Sharing Guiding Principles) is amended by adding sub-sections (vi) and (vii) as follows:

a. Clinical trials conducted by CAVD Members must be registered and information about the trial be made publicly available, through clinicaltrials.gov[8], a service of the US National Institutes of Health, agencies listed by the International Clinical Trials Registry Platform of the World Health Organization[9], or a comparable, publicly-accessible registry. Trial registration should occur prior to the start of the study and information about the registration (including the accession number and web address) shall be provided to the CAVD Alliance Manager for posting on the CAVD web site.

b. CAVD Members that generate data may need to delay sharing of data and results in the interest of protecting intellectual property rights, or because analysis of data or the primary manuscript has not been completed. Such delays will be limited to the time necessary to pursue such activities, as agreed to by the CAVD Senior Alliance Manager on behalf of the Foundation.

Following study completion, CAVD Members must provide the following:

1. **Summary Level Results.** Summary Level Results (including adverse event summaries) and a lay summary of the trial must be made available to the CAVD community no later than 6 months after study completion and be made publicly available no later than 12 months after study completion. To satisfy the requirement to share the Summary Level Results with the CAVD community the CAVD Member must provide the Summary Level Results to the CAVD Alliance Manager for posting to the CAVD members-only portal, or provide a link as to where CAVD Members can access these materials. The CAVD Member may choose the mechanism by which the Summary Level Results and the lay summary thereof are made publicly available, if a link as to where they

[8] https://clinicaltrials.gov/

[9] http://www.who.int/ictrp/en

are stored is provided to the CAVD Alliance Manager for posting to the public CAVD website. For example, CAVD Members may use existing services such as at www.clinicalrials.gov or publish the clinical trial results in an open access publication that includes a lay summary. The Summary Level Results and the lay summary do not need to be separate documents or postings if the CAVD Member can achieve the goal of clearly presenting results to a scientific and non-scientific audience with a single document or posting.

2. **Full or Abbreviated Full Data Set.** The clinical trial full data set (or abbreviated full data set) must be made available no later than 18 months following completion of the study so that other researchers can request access to de-identified or anonymized participant level data. CAVD Members are responsible for ensuring that the selected site has submission and access policies in place, utilizes an independent peer review of requests, and provides controlled access following execution of a written data use agreement. Examples of clinical data sharing sites that have such policies include, but are not necessarily limited to, www.clinicalstudydatarrequest.com and yoda.yale.org. The expense associated with sharing the full data set will be covered by the Foundation if needed. The CAVD Member must inform the CAVD Alliance Manager where the data is located and the process by which non CAVD members can access the data so that this information can be provided on the CAVD public web site.

3. **Post publication data**. For clinical trial data that is published, the Post-Publication Data Package must be shared. Sharing of the post-publication data package with information supporting the findings, tables and figures and figures of the publication also fulfills the data sharing requirement of the Foundation's Open Access Policy.

SIGNATORY

To the

CLINICAL TRIALS ADDENDUM to the CAVD DATA & MATERIALS SHARING AGREEMENT

IN WITNESS WHEREOF, the undersigned Party hereby executes the Clinical Trials Addendum to the CAVD Data & Material Sharing Agreement.

Institution

By:

Name: _____

Title: _____

Date Signed: _____

By:

Name: _____

Title: _____

Dated Signed: _____

Acknowledged by Principal Investigator:

Principal Investigator of a CAVD Project