CIMAC-CIDC Guidelines

Guidelines for data access/transfer and publications for correlative studies involving collaboration between the CIMAC-CIDC Network and the Clinical investigators/Clinical Trial Networks on NCI-supported clinical trials

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Purpose of this document: The purpose of this document ("**CIMAC-CIDC Guidelines**") is to explain the requirements involved in working with the CIMAC-CIDC Network. Specific requirements are captured in the CIMAC-CIDC Human Material Transfer Agreement (HMTA), to which your institution will be asked to formally agree.

In the Cancer Immune Monitoring and Analysis Centers and Cancer Immunologic Data Commons (CIMAC-CIDC) Network, CIMACs will perform bioassays on biospecimens from clinical trials. This CIMAC Data will be transferred from the CIMACs to the CIDC, and certain clinical data elements (described in this document) will be extracted and transferred from the National Cancer Institute (NCI)-supported Clinical Trial Network/Clinical Research Sites, hereinafter referred to as "**Provider**", to the CIDC to enable correlative analyses. CIMACs and the clinical trial investigators will work together collaboratively to conduct correlative analyses. The goal of the CIMAC-CIDC Network is to identify biomarkers with translational potential for optimizing immunotherapeutic strategies for cancer patients.

Note: All NCI-supported clinical trials utilizing the CIMAC-CIDC Network for bioassays, regardless of IND sponsor, or whether the agreement is with NCI or the Clinical Trial Network directly, will be subject to the CTEP IP Option. CIMACs, CIDC, and Provider agree to comply with the terms of the CTEP IP Option and provide rights to NCI/Pharma Collaborators to data and inventions generated from the use of the Human Material. The Provider will be responsible for ensuring that all agreements between Pharma Collaborators and Provider acknowledge that the CIMAC research project is subject to the terms of these CIMAC-CIDC Guidelines and the CIMAC-CIDC Human Material Transfer Agreement (HMTA). Additionally, these agreements must be shared with the NCI CTEP Regulatory Affairs Branch (NCICTEPACG@mail.nih.gov) prior to signature for review and confirmation.

This document addresses the following processes:

- Clinical Data and CIMAC Data transfer to CIMAC-CIDC
- Biomarker data repository and access
- Review process with NCI and NCI/Pharma Collaborator(s) and guidance for authorship of publications involving data deposited into CIDC

Important notes regarding biospecimen transfers:

Biospecimens should not be transferred to the CIMACs until the following occur:

- CTEP has approved the Research Project.
- The CIMAC-CIDC Human Material Transfer Agreement (HMTA) has been signed.
- Any required protocol amendments have been approved by NCI.
- Any Provider/ Pharma Collaborator agreements related to the Research Project have been reviewed and approved for compliance with the Guidelines.

Definitions:

"**Agent**" means an investigational drug, a biologic, or a product proprietary to a NCI/Pharma Collaborator, that has been made available under an agreement between NCI/Pharma Collaborator and National Cancer Institute (NCI) or a Clinical Trial Network and used in association with a NCI-supported clinical trial.

"**Biospecimens**" means blood, serum, urine, saliva, other bodily fluid, bone marrow, cells, stool, or tissue samples/specimens collected under a Protocol from Human Subjects. The term "Biospecimen" further includes, without limitation, any tangible material derived from such Biospecimens collected under the Protocol from Human Subjects, such as genes, gene fragments, gene sequences, proteins, protein fragments, protein sequences, DNA, RNA, and any subcellular structure, and their unmodified derivatives.

"**CIDC**" means the Cancer Immunologic Data Commons, hosted at Dana-Farber Cancer Institute, Inc. The CIDC will serve the bioinformatics needs of the CIMACs, including the provision of a centralized data repository, optimization of data collection methodologies suitable for immune-related biomarkers, data integration, and provision of a shared infrastructure for integrative and correlative analysis.

"**CIMAC Data**" means CIMAC-generated data including, but not limited to, assay output and data on assay validation and performance using clinical trial samples. The CIMAC Data will be jointly owned by the Provider and the CIMAC that generated the data from the Human Material. The CIMAC will own the data they generate that do not relate to a Research Project (for example, improvements to assays that are not directly related to specific Human Material).

"**CIMACs**" means the four Cancer Immune Monitoring and Analysis Centers, (1) Dana-Farber Cancer Institute, Inc., (2) Leland Stanford Junior University (Stanford University), (3) the University of Texas MD Anderson Cancer Center, and (4) the Icahn School of Medicine at Mount Sinai, which are responsible for providing a wide range of bioassays on Biospecimens from Human Subjects enrolled in clinical trials.

"**CIMAC-CIDC**" means the network composed of the four CIMACs and the CIDC supported by NCI U24 Cooperative Agreements to provide an infrastructure to support correlative studies in clinical trials involving immunotherapies, including Cross-Trial Analysis. The goal of this research is to identify biomarkers with translational potential for optimizing therapeutic strategies for the treatment of cancer.

"**CIMAC-CIDC Principal Investigators**" means those individuals listed as Principal Investigators or Co-Principal Investigators on the NCI Grant for the CIMAC or CIDC.

"**CTEP**" means the Cancer Therapy Evaluation Program, of the Division of Cancer Treatment and Diagnosis (DCTD), which is a program within NCI that plans, assesses, and coordinates all aspects of clinical trials, including extramural clinical research programs, internal resources, treatment methods and effectiveness, and compilation and exchange of data. NCI is part of the National Institutes of Health (NIH), a component of the U.S. Department of Health and Human Services (HHS).

"**CTEP IP Option**": The CTEP Intellectual Property (IP) Option applies to all NCI-supported clinical trials, regardless of the IND sponsor, and to all CIMAC-CIDC Research Projects. All inventions resulting from the Research Projects are subject to the terms of the CTEP IP Option, which can be found at:

(a) http://ctep.cancer.gov/industryCollaborations2/guidelines_for_collaboration.htm, or
(b) The Federal Register, Vol. 76, No. 48, pages 13404-13410 (2011) (https://www.gpo.gov/fdsys/pkg/FR-2011-03-11/pdf/FR-2011-03-11.pdf)

"**Clinical Data**" means data collected from Provider on the Protocol: demographics; pathology and staging; pathology reports; outcome data; toxicity; study treatments; prior molecular data (if captured); prior therapies (if captured); Required Clinical Data Elements (defined below); and information on the Specimen Tracking Manifest.

"**Clinical Investigator**" means, in accordance with 21 C.F.R. § 312.3, an individual who directs the administration or dispensation of Agent to a Human Subject, and who assumes responsibility for studying the Human Subjects under the Protocol, for recording and ensuring the integrity of research data, and for protecting the welfare and safety of Human Subjects, at a Clinical Research Site.

"**Clinical Research Site(s)**" means the site(s) at which the applicable Protocol will be performed.

"**Clinical Trial Network**" means the NCI-supported clinical research network participating in the Research Project. This could be the Experimental Therapeutics Clinical Trials Network (ETCTN), a Network Group of the National Clinical Trials Network (NCTN), the Cancer Immunotherapy Trials Network (CITN), and/or another network/consortium supported by NCI.

"**Clinical Trial Team**" means investigators from the clinical trial and the Provider, such as the trial principal investigator (PI), statistician, and translational leaders.

"**Correlative Study Analysis Team**" means the collaborative team comprised of Clinical Trial Team and CIMAC-CIDC investigators involved in the design and execution of the Research Project.

"**Cross-Trial Analysis**" means analysis with data obtained from more than one clinical trial.

"**Embargo Period**" means the period during which data generated from a clinical trial supported in whole or in part by NCI will be held in confidence for use only by the Clinical Trial Team, Correlative Study Analysis Team, CIMAC-CIDC Principal Investigators, and any relevant NCI/Pharma Collaborators. The Embargo Period will be in effect until six (6) months after the primary outcome of the trial is either published in manuscript form or, if there is no publication, six (6) months after the results are posted to ClinicalTrials.gov. The Embargo Period may be extended on NCI/Pharma Collaborator request to NCI.

"**Human Material**" means the Biospecimens, and/or any Clinical Data or other information (including information on the Specimen Tracking Manifest and the Required Clinical Data Elements) collected under the Protocol, that are transferred by the Provider to the CIMAC-CIDC.

"**Human Subject**" means, in accordance with the definition in 45 C.F.R. § 46.102(f), a living individual about whom a Clinical Investigator conducting research obtains:

a) data through intervention or interaction with the individual; or
b) Identifiable Private Information (private information about a Human Subject from which the identity of the subject is or may readily be ascertained. Regulations defining and governing this information include 45 C.F.R. Part 46 and 21 C.F.R. Part 50).

"**NCI/Pharma Collaborator**" means a company that made available its Agent(s) for use in association with the Protocol(s). This includes agreements with NCI and/or directly with a Clinical Trial Network/Clinical Research Site.

"**Non-CIMAC Data**" means assay data transferred to the CIDC from an outside (non-CIMAC) lab to be used in the analysis of the CIMAC Data and/or Clinical Data.

"**Protocol**" means the Institutional Review Board ("IRB")-approved clinical trial under which the Human Material was collected, in which an Agent was administered or dispensed to, or used involving, one or more Human Subjects. It describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The term "Protocol" includes any and all associated documents, including informed consent forms.

"**Provider**" means the Clinical Trial Network/Lead Academic Organization/Clinical Research Site, as applicable, providing, or authorizing the provision of, the Human Material to CIMAC-CIDC.

"**Required Clinical Data Elements**" **or** "**RCDE**" are a subset of the Clinical Data. RCDE are comprised of 1) the Clinical Data required to perform the Research Project, including all variables and endpoints as specified in the NCI-approved Research Project, as well as 2) demographics; prior therapies (if captured); pathology; pathology reports; and information on the Specimen Tracking Manifest.

"**Research Project**" means the specific, NCI-approved correlative studies related to the Protocol and described in each NCI-approved biomarker plan collaboratively developed by the Correlative Study Analysis Team.

"**Research Proposal**" means the proposal developed by the Correlative Study Analysis Team which serves as the basis for internal review and tracking by the CIMAC-CIDC Network and NCI. Once approved by NCI, the proposed study becomes the Research Project.

"**Results**" means all information generated by the integrative analysis of the CIMAC Data and Clinical Data by the Correlative Study Analysis Team using the Human Material under the Research Project.

"**Specimen Tracking Manifest**" refers to a secure web-based method for sharing Human Subject demographics, clinical reports, specimen tracking, sample processing, and specimen quality assurance information.

Guidelines:

1. Collaboration

The work to be performed within the CIMAC-CIDC is a collaboration between the Clinical Trial Team and the CIMAC-CIDC investigators throughout the translational study process, from study design, bioassays and correlative analyses, to publications.

The senior statistician from the clinical trial will be included among the clinical trial representatives and will collaborate with the CIMAC-CIDC statistician on the correlative study(ies) in which the CIMAC-CIDC is involved.

2. Data Access, Use, and Sharing

a. Transfer of Clinical Data to the CIDC

Use of the CIMAC-CIDC resource will require Provider to agree to transfer the Clinical Data to the CIDC. The CIDC is intended to be the Clinical Data repository for correlative studies using the CIMAC-CIDC.

i. **Timing of sending RCDE to CIDC:** To enable correlation of biomarker analyses with Clinical Data, **all Required Clinical Data Elements (RCDE) must be transferred to the CIDC before the final CIMAC Data can be made available to the Correlative Study Analysis Team** (i.e., including the Clinical Trial Team). Once the clinical annotation required for CIMAC biomarker correlative analysis is provided to the CIDC, the Correlative Study Analysis Team (including the Clinical Trial Team) can access the assay data via the CIDC.

ii. **Timing of sending the remaining Clinical Data to CIDC:** Use of the CIMAC-CIDC requires agreement to transfer all Clinical Data to the CIDC as soon as possible following clinical trial database lock or trial completion, but no later than 6 months after primary publication of the trial or, if there is no publication, six (6) months after the results are posted to ClinicalTrials.gov.

iii. The timing of the transfer of Clinical Data to CIDC will not affect transfer of Clinical Data to the clinical trial's NCI/Pharma Collaborators.

iv. As the CIDC matures, informatics tools will be developed to streamline data transfer. However, the lack of such tools at the outset should not interfere

with the submission of the Clinical Data using existing, available, and agreed-upon transfer tools between Provider and the CIDC.

v. Clinical Data transferred to the CIDC must be kept confidential and are subject to data use restrictions (described in Section 2.c).

vi. The Clinical Data will only be used to perform correlative studies described in NCI-approved Research Projects, or for improvement of assay performance and/or selection of assays.

b. Access to and use of CIMAC Data, Clinical Data, and Results in CIDC for correlative analysis by the Correlative Analysis Team

i. The CIMACs will ensure that CIMAC Data are submitted to the CIDC as soon as available, and, if requested, also shared with NCI.

ii. The CIDC will serve as the data repository for CIMAC Data, for Clinical Data, including RCDE, and for Results, and will provide the informatics platform for the analysis by the Correlative Study Analysis Team to generate the Results.

iii. The CIMAC-CIDC will be responsible for notifying the Clinical Trial Network/Clinical Trial Team of the availability of the CIMAC Data and Results, as soon as they are available in the CIDC. Non-CIMAC access to the Results made be delayed if any RCDE has not be provided to the CIDC.

iv. The Correlative Study Analysis Team will use the platform provided by the CIDC to perform their correlative analyses. The CIDC may also provide analytical tools for data analysis within the CIDC portal and CIDC cloud infrastructure.

c. Data security, Embargo Period, and Human Subject Protections

i. The Correlative Study Analysis Team will access the CIMAC Data, any transferred Clinical Data, and Results within a confidential, secure environment in the CIDC. These data must be kept secure and confidential and comply with data use restrictions as defined below:

- The CIMAC Data, Clinical Data, and Results should not be released to any entity or individual outside the Correlative Study Analysis Team or outside of permissible intra-CIMAC-CIDC network sharing. (Please see Section 2f, below, regarding the terms of permissible intra-CIMAC-CIDC network data sharing.)
- All data accessed through the CIDC will be accessed and used only on a device with security controls adequate to protect sensitive identifiable information. Only approved persons will have access to the data, and control over the data will be maintained at all times. Hard copies of any

data must similarly be stored under conditions sufficiently secure to avoid inappropriate access, and must be shredded prior to discarding.

ii. An Embargo Period will be in effect during which all data generated from a clinical trial supported in whole or in part by NCI will be held in confidence for use only by the Clinical Trial Team, Correlative Study Analysis Team, CIMAC-CIDC Principal Investigators, and NCI/Pharma Collaborator(s). The Embargo Period will be in effect until 6 months after the primary outcome of the trial is either published in manuscript form or, if there is no publication, 6 months after the results are posted to ClinicalTrials.gov. The Embargo Period may be extended on request by the NCI/Pharma Collaborator, with NCI approval.

iii. <u>During the Embargo Period</u>, Clinical Data, or Results and CIMAC Data pertaining to Clinical Data in the CIDC will not be published by CIMAC-CIDC investigators without the permission of the NCI and the Provider.

iv. Prior to the end of the Embargo Period, NCI will contact the NCI/Pharma Collaborator to determine if an extension of the Embargo Period for regulatory filing is required.

v. <u>Following publication of the Results</u> in a manuscript, and while the Embargo Period is still in effect, the CIMAC-CIDC investigators may perform additional analysis of the Results with approval from the relevant Clinical Trial Team(s)/Clinical Trial Network, NCI, and NCI/Pharma Collaborator. These additional analyses will require submission of a proposal to NCI describing the proposed analyses.

vi. <u>After the Embargo Period</u>, CIMAC-CIDC investigators may use the available data for all other analyses by following the procedures described in the "Data-sharing post-Embargo Period" Section below.

vii. Any analyses of data, and any use of the Clinical Data or Results, that are planned for publication, including via manuscripts and abstracts, will be submitted to NCI for review and comment by CTEP and the NCI/Pharma Collaborator, and, if a proposal is for Cross-Trial Analyses, approval, by CTEP, the relevant NCI/Pharma Collaborator(s), and the Provider.

viii. CIMAC-CIDC will abide by all applicable regulations regarding Human Subject Protections.

d. Use of data by NCI/Pharma Collaborator

i. NCI/Pharma Collaborators have the right to use all Clinical Data, CIMAC Data, and Results, for internal use and regulatory filings related to the development and commercialization of their Agent(s) (see Section 2h, below).

ii. As appropriate, NCI or Provider will share Clinical Data, CIMAC Data, and Results with NCI/Pharma Collaborator.

e. Data ownership

i. The CIMAC and Provider will jointly own the Results, as well as the CIMAC Data generated from the Human Material. The CIMAC will own the data they generate that do not relate to a Research Project (for example, improvements to assays that are not directly related to specific Human Material).

ii. The Provider will maintain ownership of the Clinical Data, including the RCDE.

f. Cross-Trial Analysis

Cross-trial Analysis as well as confidential, internal sharing of data between the CIDC and the CIMACs is permitted among CIMAC-CIDC Principal Investigators **for purposes of improvement of assay performance or selection of assays**. The analysis will not, however, be publicly disclosed (through publication or otherwise), without the express, written approval of NCI, and review by the relevant NCI/Pharma Collaborator(s) and Provider(s).

Cross-trial Analysis **for research questions**, i.e., beyond purposes of assay improvement/assay selection, will require a written proposal to be reviewed and approved by NCI, and, if Clinical Data or Results are used, the relevant NCI/Pharma Collaborator(s) and Provider(s). All resulting publications from any Cross-Trial Analysis will be submitted to NCI for review in accordance with the "Publication guidelines" section below.

Following the Embargo Period, the CIMAC Data, Clinical Data, and Results will be submitted to the controlled-access CIDC for sharing with approved requestors from the general research community (see Section 4, below).

g. Non-CIMAC Data

For certain trials, Non-CIMAC Data of sufficient quality may be transferred to the CIMAC-CIDC and added to the CIMAC Data to enhance the correlative analyses, depending on the compatibility of the data format and objectives of study projects. In receiving Non-CIMAC Data, the CIMAC-CIDC would be required to treat the non-CIMAC Data in the same manner as Clinical Data for the purposes of confidentiality, use, and publication. Non-CIMAC Data could include prospective or retrospective assay data.

h. Inventions using data generated by use of Human Material from an NCI-supported clinical trial

A responsible approach to management of intellectual property derived from any downstream discoveries that is consistent with the recommendations of the NIH's

Best Practices for the Licensing of Genomic Inventions and the NIH Research Tools Policy is encouraged.

The management of patent applications in a manner that might restrict use of the joint findings and that could substantially diminish the value and public benefit provided by these resources is discouraged. However, if the Biospecimens proposed for a Research Project are from a clinical trial that was conducted under a binding collaborative agreement with NCI/Pharma Collaborator, or was otherwise supported by NCI, they are subject to the terms of the CTEP Intellectual Property (IP) Option (http://ctep.cancer.gov/industryCollaborations2/guidelines_for_collaboration.htm) as well as the terms of the CTEP or Clinical Trial Network Collaborative Agreement under which the study is conducted. Any discoveries from research performed on Biospecimens collected in NCI-supported trials will be subject to the CTEP IP Option.

For avoidance of doubt, a NCI/Pharma Collaborator who has rights to an invention under the scope of the CTEP IP Option also has the right (a commercial non-exclusive, royalty-free license) to use any data generated in such studies for regulatory filings related to the development and commercialization of the Agent.

3. Publication guidelines

a. Authorship:

Correlative studies using the CIMAC-CIDC resources are collaborative efforts between the CIMAC-CIDC and the Clinical Trial Teams. **All publications based on CIMAC Data should recognize this collaboration, through authorship, consistent with general authorship guidelines for collaborative work and mutually agreed upon by all parties.**

While a given project may have specific arrangements regarding authorship, some general guidelines can be considered, as follows:

i. **Manuscript/abstract on primary clinical outcome in which CIMAC-CIDC work involves correlative markers:** Generally, if ancillary biomarker endpoints are included in the primary manuscript for the clinical outcome, the PIs leading the trial (and the statistician analyzing the trial) will have the lead authorship roles. CIMAC-CIDC investigators will be included as co-authors or co-lead-authors depending on their specific collaboration in accordance with the level of contribution to the research.

ii. **Non-primary-outcome manuscripts/abstracts of the trial in which CIMAC-CIDC work generates the main findings:** For secondary abstracts/manuscripts that report primarily correlative results, it may be appropriate that CIMAC-CIDC lead investigators/statisticians have the lead or co-lead authorship roles. However, each situation is unique and will have to be agreed upon by all of those collaborating in the study.

iii. **CIMAC-CIDC-initiated Cross-Trial Analysis (i.e., across multiple trials):** Depending on the primary purpose of the Cross-Trial Analysis, the Clinical Trial Network/Clinical Trial Team and CIMAC-CIDC will have to come to agreement on authorship roles. Clinical and CIMAC-CIDC investigators will be included in accordance with their level of contribution to the research.

b. Publications

All manuscripts, abstracts, presentations, or posters arising from CIMAC-CIDC studies must be sent to CTEP at NCICTEPpubs@mail.nih.gov no later than thirty (30) days before submission for proposed manuscripts and seven (7) days before submission for proposed abstracts or disclosure for presentations. NCI will send the submission or disclosure for advisory review and comment by CTEP staff, by NCI/Pharma Collaborator, and, during the Embargo Period, by the Correlative Study Analysis Team and the Clinical Trial Network/ Provider.

The NCI/Pharma Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that the NCI/Pharma Collaborator(s)'s confidential and proprietary data, in addition to the NCI/Pharma Collaborator(s)'s intellectual property rights, are protected.

In all oral presentations or written publications arising from the use of Human Material, CTEP, NCI/Pharma Collaborator, CIMAC-CIDC, and Provider will be acknowledged unless requested otherwise.

Press releases and other media presentations must also be forwarded to CTEP (at NCICTEPpubs@mail.nih.gov) at least five (5) days prior to release for review by NCI and other parties as needed.

Note: While NCI/Pharma Collaborator comments are not binding, authors must address all comments made by NCI/Pharma Collaborator. However, information proprietary to the NCI/Pharma Collaborator must be redacted at the NCI/Pharma Collaborator's request.

4. Data-sharing post-Embargo Period

a. The CIMAC-CIDC data sharing plans will be consistent with the guidelines in the NIH Genomic Data Sharing Policy: https://www.cancer.gov/grants-training/grants-management/nci-policies/genomic-data

b. At the end of the Embargo Period, the CIMAC Data, Clinical Data, and Results will be available in the controlled-access CIDC for sharing with approved requestors from the general research community. Each requestor (whether intramural or extramural) will submit a proposal that will be shared with the NCI/Pharma Collaborator for a review and comment period of 4 weeks. Requestors will be required to execute a NCI Data Use Agreement (DUA) prior to receiving the requested data. All such DUAs will contain terms providing to the NCI/Pharma Collaborator: 1) manuscript review, 2) the CTEP IP Option, and 3) the data use rights as granted to the NCI/Pharma Collaborator in any

applicable agreements with the NCI/Pharma Collaborator. A summary of the requests received for the CIMAC Data, Clinical Data, and/or Results from the Protocol(s) can be provided to the Provider. These requirements are in addition to those for the NCTN/NCORP Data Archive.

c. Data sharing must also comply with the data-sharing requirements as described in the Requests for Applications (RFAs) for the CIMACs and CIDC, found at the links below:

https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-005.html
https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-006.html