COVADIS Microvascular Angina Registry - Policy and Procedures

I. Statement of General Policy Guidelines:

The policy and procedures adopted by the COVADIS investigators for the utilization of COVADIS Microvascular Angina Registry data are intended to protect the interests of all study participants, to assure that study data conform to the required study objectives and are accurately presented, that authorship is appropriate, that communications which are to become part of the permanent public record are well-written, that all investigators are aware of ongoing projects, to avoid unnecessary duplication of analysis and to ensure that publication or presentation of COVADIS data does not occur without approval of the Steering Committee.

In general, the general policy of the COVADIS Steering Committee and study group will be directed by the Mission Statement:

COVADIS Mission Statement – the Coronary Vasomotor Disorders Summit (COVADIS) is an independent global working group aiming to:

a. Raise awareness of Coronary Vasomotor Disorders at all levels of the coronary circulation and their contributions to myocardial ischemia.
b. Standardize international nomenclature, diagnostic criteria and therapeutic strategies for Coronary Vasomotor Disorders.
c. Promote Coronary Vasomotor Disorders research via registries, translational and clinical studies and trials.

1a. Membership and Rules of Order:

The Registry Committee will consist of the founding investigators of the COVADIS study group, broadly representative of international investigators with area expertise, including representatives from Australia (1), Italy (2), Japan (2), Germany (2), UK (1) and USA (1). Within the Steering Committee, Co-Chairs are John Beltrame, AU; Noel Bairey Merz USA, and DCC PI Hiro Shimokawa, JP.

The Registry Committee will operate in a consensus mode relative to the formulation of all policy and publication decisions. The Registry Committee will meet regularly to review the status of study policy and publications. A summary of these meetings will be recorded by the COVADIS co-chairs or designees. These summaries will be distributed to the Registry Committee in advance for review and approval at the next Steering Committee or general COVADIS meeting. Upon approval these summaries will constitute part of the permanent record of the COVADIS project maintained by the COVADIS co-chairs and Steering Committee.

1.b. Human Subjects Research. All COVADIS clinical research activities (registries, data bank, ancillary, clinical trials) will adhere to appropriate human subjects research policy, and each site and data coordinating center (DCC) will obtain ethical review board approval. Copies of each site and DCC ethical review board approval will be maintained in the respective COVADIS registry site and the DCC. If Data Transfer Agreements are needed, the DCC will obtain these for the needed sites.

1.c. Research Subject Confidentiality. Confidentiality is vigorously maintained. The clinical sites will conduct annual follow-up calls. Subject names are encoded into alphanumeric IDs upon entry at the clinical sites. Subject names do not appear on any documents or data submitted to the DCC.

Additionally, the data base management system protects data files against inadvertent change or access by non-project personnel through the use of passwords and file protection systems. File protection layers within the database allow individuals to "read" data without the ability to write or change data.

1.d. Withdrawal of Investigators from COVADIS. Investigators and sites may withdraw from the COVADIS Microvascular Angina Registry. Data submitted prior to withdrawal, as anonymized subject data, will be retained in the COVADIS Microvascular Angina Registry with no further site follow-up, unless the specific research subject requests that their data no longer be used.

1.e. Clinical Studies and Trials Data and Safety Monitoring: Although the current COVADIS registry is not a phase III clinical trial, COVADIS will have a Data Integrity Monitoring Board (DIMB) who's function is to (a) ensure data governance – i.e. sites have ethics approval and data is handled confidentially, (b) data audits – 5% of data audited for internal consistency (we are unable to validate with original records unless we have funding support), and (c) independent review of complaints. The DIMB will include expertise in cardiology, imaging and biostatistics. Annual and interim telephone conference calls will be convened. The DCC will prepare reports of study progress and provide information about adverse events possibly related to participation.

2. General Statement of Editorial Policy:

It is anticipated that COVADIS will generate considerable new data relative to the identification, evaluation and management of vasospastic angina (VSA), coronary microvascular dysfunction (CMD) and other ischemic heart disease conditions. One purpose of this Steering Committee is to foster and guide development of scientific reports originating from such data obtained from the COVADIS project. The scientific integrity of the project requires that all merged data from all COVADIS sites be analyzed study wide and reported as such. Thus, an individual site is expected not to report and publish data collected from its site related to the fundamental goals of the COVADIS study alone or under the by-line of the COVADIS study. Specifically, an investigator can independently publish their site data provided it does not use or infer that it was COVADIS; for areas of overlap or potential controversy, the Steering Committee and Chief Investigator will review and develop a consensus decision based on scientific merit. Development of ancillary studies or data bank studies dealing with specific analyses are encouraged in order to optimally utilize the expertise available for the COVADIS project. All presentations and publications of any type based upon data from these studies are expected to maintain the integrity of the objectives of the overall project. The Registry Committee will prepare recommendations concerning the timing of data analyses for these summaries, presentation of main response variable data (diagnostic/prognostic outcome data) including manuscripts on design and methods and designation of the meetings at which they might be presented. By agreement of the Steering Committee, primary response variable data related to the fundamental goals of the COVADIS study alone or under the by-line of the COVADIS study, even when related to site-specific tests/technologies, will not be presented prior to the release of the main results and approval by the Committee. An exception to these recommendations would be site specific data from the pilot phase.

When studies are conducted on COVADIS subjects by investigators outside of the COVADIS study group, representation on reports of these subjects by COVADIS investigators who have contributed to the study shall be assured prior to the finalization of these studies. The writing group will develop the request for data analysis as well as the abstract or manuscript reporting

these data. These reports will be reviewed by the Steering Committee.

3 Submission of Proposals:

Before beginning an outcome, data bank, parallel, or ancillary study, a proposal initiated by one or more of the COVADIS investigators and/or their associates must be submitted to the Registry Committee. Each proposal should be no more than three pages and include the following:

1. Background summary
2. Clear statement of objectives or research hypotheses
3. Brief description of data to be used
4. Description of methods or analyses
5. Proposed collaborators
6. Sources of funding

Full details should be given concerning any procedures to be carried out on study subjects such as genetic testing, specimen disposal, radiological procedures, etc. that are not detailed or included in the original COVADIS registry consent and ethical review board approval. Any substances to be injected or otherwise administered must be identified. Any observations to be made or procedures to be carried out on a subject outside of a COVADIS site should be described. The extent to which a data bank or ancillary study will require additional clinic visits by the subjects should be detailed. Information should be given concerning the extent to which the ancillary study will require biological (blood, urine, tissue) specimens. If biological specimens are to be obtained, all procedures to be carried out on these specimens should be specified. Specifically, proposal submission and COVADIS review is not binding, but aimed to address any potential ethical review board oversight/confusion, as well as obtain scientific advisement from the COVADIS group.

The template for the COVADIS data request is included in the Appendix.

Two copies of each proposal should be submitted to the COVADIS DCC PI, co-chairs, and the Steering Committee for inventory and review. The review process will involve two reviewers within the Steering Committee and from the Chief Investigator Committee who will review the proposal and initiate discussion at the next Steering Committee meeting. On the basis of this discussion a consensus should be reached. The co-chairs will notify the Investigator(s), through the DCC by written memorandum whether the project is approved, disapproved or additional information is needed before a recommendation can be made. The COVADIS Microvascular Angina Registry DCC PI (Shimokawa) will approve/disapprove data and/or data analysis requests that are un- or under-funded, e.g. a burden on the DCC resources.

4. Authorship:

The publication(s) pertaining to the fundamental goals (outcomes) of the COVADIS project involving subjects enrolled in COVADIS will have authorship identified by the Steering Committee and a Chief Investigator Committee where membership is determined by COVADIS Registry participation, using the byline 'the COVADIS Study Group'. An appendix listing all contributing principle and co-Investigators in COVADIS will be included at the end of the initial manuscript's text or appendix. It is intended that there will be more than one publication concerning the major goals; these publications will list the writing team as the authors on behalf of the COVADIS Study Group and reference the appendix listed in the initial text. The same guidelines will apply to reports of COVADIS parallel, data bank and ancillary studies.

When the publication(s) utilize merged COVADIS data from the DCC (multi-center data), an author from each submitting COVADIS site should be given the opportunity to be a co-author.

Each author must have contributed significantly to the submitted work. Authorship is considered to include all of the following: 1) conception and design or analysis and interpretation of data, or both; 2) drafting of the manuscript or revising it critically for important intellectual content; and 3) final approval of the manuscript submitted. Participation solely in the collection of data does not justify authorship but may be appropriately acknowledged in the Acknowledgement section.

5. Review and Approval of Manuscripts and Abstracts Prior to Presentation and Publication:

The Registry Committee will review all COVADIS data bank study abstracts and manuscripts prior to submission for publication or presentation. All abstracts must be received by the Registry Committee members, all co-authors, and the Data Coordinating Center (DCC) at least one month prior to the submission deadline. Abstracts will be cross-checked against previous abstracts and papers to identify and eliminate any inconsistencies or duplicate publications.

Each manuscript considered suitable for publication will be submitted to a Chair of the Registry Committee who is responsible for arranging and implementing review according to the following procedures.

1. The manuscript will be forwarded promptly to at least two reviewers selected from the members of the Registry Committee, associates or specific consultants, with the request to respond within two weeks with a detailed critical review of the manuscript. Outside reviewers may be selected when appropriate.
2. Reviews will be forwarded to all members of the ad hoc Writing Subcommittee without the reviewers being identified, with a request for appropriate revision and response.
3. The Writing Subcommittee will be expected to respond to the review in a reasonable period of time, forwarding to the Registry Committee Chair and the DCC the revised manuscript and a letter commenting in detail on the points raised by the reviewers.
4. After review, the Steering Committee will decide, in consultation with the DCC, if release for publication is appropriate.
5. Through the DCC, the Chair of the Registry Committee will then notify the authors by memorandum, the COVADIS Steering Committee of its decision within one month of the receipt for a manuscript, within one week for abstracts. All manuscripts or abstracts approved for submission will be submitted 'on behalf of the COVADIS study group'.
6. An email review may be used when the Steering Committee is not meeting in a timely fashion. All submissions must be sent to the co-chairs who will distribute the materials to the Steering Committee. A quorum of the co-chairs, Registry Committee member, and DCC PI is needed for approval.

6. Intellectual Property

The Registry Committee agrees that any intellectual property (patents, royalties) resulting from the COVADIS CMD Registry maintained by the DCC PI (Shimokawa) belong to the DCC PI (Shimokawa).