APPENDIX 8. Guide for External Researchers Requesting Data and Sample Sharing Collaboration with the PREDIMED PLUS Study

Those of us associated with the PREDIMED PLUS study are aware that a focus on collaborative research is advantageous to researchers, who can collaborate on several studies and contribute to the generation of joint benefits.

Researchers who are affiliated with research organisations and who are investigating topics related to the objectives of the PREDIMED PLUS study can request collaboration with the PREDIMED PLUS researchers in order to gain access to particular samples and data generated during the study.

Special value will be given to collaborations with relevant and novel objectives, and to those where the collaborating researcher could provide other data for comparative purposes or increase the sample size. Proposals to evaluate highly speculative hypotheses or those with ethical restrictions will not be considered appropriate.

Because the numerous groups that are part of the PREDIMED PLUS study already produce a high level of internal demand for data analysis, proposals submitted by external researchers must be clearly justified, and must not overlap with similar proposals already in progress and being performed by internal researchers, or those that appear as objectives of the various research projects approved by the Steering Committee.

Furthermore, because a finite number of samples have been collected, and since the numerous groups that are part of the PREDIMED PLUS study produce a high level of internal demand for sample analysis, proposals submitted by external researchers must be clearly justified, and must not overlap with similar proposals already in progress and being performed by internal researchers, or those that appear as objectives of the various research projects.

For sharing of both data and samples with external researchers, authorisation will have to be received from the PIs from each node that collected those data/samples from the corresponding patients.

Collaboration proposals may be submitted for both general data/samples from the PREDIMED PLUS study and for specific projects. In the case of specific projects, the coordinator of the corresponding specific project must be the one maintaining the most direct contact with the external researcher submitting the collaboration request.

1. Submission of a collaboration proposal

The following steps must be followed in order to submit a proposal for collaboration and access to data:

1.1. Production of a collaboration request letter:

This letter is addressed to the Steering Committee for the PREDIMED PLUS study (predimed_plus_scommittee@googlegroups.com), and in it the investigator must provide a general description of the collaboration request, along with a brief CV summarising his or her research activities. The benefits of the collaboration must also be described (see further details on the form attached as APPENDIX 7. Collaboration Request Form for Outside Researchers).

1.2. Completion of the collaboration request form for outside researchers for the PREDIMED PLUS study, in order to access data and samples generated during the PREDIMED PLUS study.

This form is also used to submit further details about the study: hypothesis, objectives, methodology, variables requested, sample size, duration of the study, etc.

2. Submission and evaluation of the proposal

The proposal must be submitted electronically to the Steering Committee for the study during the first week of each month. Each proposal will be assessed and assigned a status: accepted, corrections needed, or rejected.

The basic criteria used to evaluate the proposals will be the following:

- The scientific excellence of the proposal
- The strategic priority of the proposal, with respect to the PREDIMED PLUS studies in progress, in order to avoid unnecessary duplication of work
- The scientific research background of the person or group submitting the request
- The scientific quality and capacity to administer the project
- The proposed study's compliance with the contents of the informed consent form signed by the participants whose data is being requested
- The number of samples requested and viability of making them available

3. Conditions for access to data requested from the PREDIMED PLUS study

If the proposal is accepted, a **Collaboration Agreement** (*Appendix 9*) will first need to be signed. This document contains details on the terms and conditions under which access to the requested data is being granted, and these terms and conditions must be accepted by the collaborating researcher. New authorisation from the PREDIMED PLUS study's Ethics Committee may also be required, depending on the type of study proposed (the centralised committee or those from the various recruiting nodes from which data are being requested).

Because the PREDIMED PLUS study does not currently have a data management system based on data enclaves, which would give external researchers the ability to access data for the variables in securely but without the ability to modify or copy them, some additional requirements must be specified in order to ensure the security, integrity, and confidentiality of the data.

External researchers who are only requesting data will be given a password which is used to access a data file that contains the variables requested. In order to better protect the identities of the participants, this data file is anonymised, without any variables that could serve as identifiers. The corresponding metadata will also be provided. However,

when an external researcher is requesting data and samples at the same time, an identifier is required to connect the data from the determinations performed on the samples with the data file for the patient. The PREDIMED PLUS ID appears on the freezer tube used for samples, and this ID would provide direct access to the patient's identity. Therefore, in order to minimise this risk, the external researcher must provide this data to a collaborating researcher from the PREDIMED PLUS study after the samples have been analysed. The internal researcher will then merge the files containing the sample determinations with the rest of the data required, and then provide the external researcher with this merged data file that does not contain any identifiers.

Outside researchers must make a commitment to:

- refrain from attempting to identify the individual patients, while maintaining confidentiality.
- maintain the integrity of the data and samples.
- maintain secure environments for storage of data and samples.
- refrain from distributing the data to unauthorised third parties.
- use the data provided only in relation to the specific objectives for the collaboration.
- use the samples exclusively for the determinations approved in the PREDIMED PLUS study, with no permission to perform additional determinations or transfer the samples to other researchers.
- return any remaining samples after the determinations have been completed, under optimal conditions of preservation.
- submit a copy of the results from the determinations performed to the central database for the PREDIMED PLUS study, or to the federated database that will be designated for this purpose if there are technical restrictions on the formats, in order to allow that data to be incorporated after the work period has ended, which is established as 2 years after reception. *In exceptional cases it will be possible to request an extension.*.
- provide each node with a copy of the data corresponding to the samples each node provided whenever a paper is produced using determinations performed on samples from multiple nodes.
- destroy the data provided at the end of the active establishment period for the Collaboration Agreement.
- adhere to the publications policy.

4. Data analysis and publications

The external researcher must ensure the quality of the statistical analyses performed as well as application of best practices. Details must be provided on the software used, and the syntax must be saved and delivered, along with the data, to each node that provided samples used for the determinations.

It will not be possible to authorise new papers for nodes other than the one performing the determinations, until the paper corresponding to that data analysis has published, and unless this takes place in collaboration with those generating the data.

In the case of proposals for **meta-analysis**, the statistical analysis will be performed by an internal researcher from the PREDIMED PLUS study, who will be assigned based upon the experience required for the collaboration, and in this case the aggregate results requested will be provided in the form of tables.

The publication proposal form must be completed, including the names of the authors of the publication(s). In the case of original studies, the publications policy will be followed when establishing authorship, taking into account whether the collaboration involves data from the general study and for the total sample, or if specific projects are involved.

The publication proposal must be approved by the Steering Committee, and the results in the form of tables and the full article must be submitted before they are sent out for publication, so that the appropriate quality controls can be performed.

5. Cost

The procedures carried out by the researchers from the PREDIMED PLUS study have a cost in terms of their time, including their review of the data access request, preparation of the data, provision of access to the data and metadata, statistical analyses in some cases, and review of the publication proposal and results. Therefore, like other large international groups have done, a fee is being established in relation to data access, which will be collected after a data request has been approved. A bank transfer can be used to deposit this amount into the PREDIMED PLUS account opened for this purpose, or payment can be made using a credit card. Depending on the type of collaboration involved, this fee would vary from situations with full exemption up to a cost of €12,000 (*see document on "Fees for data and samples"*).