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| **Saw Swee Hock School of Public Health****Data Management** | **SOP:** | **SSHSPH-DM-B001-16-V2.0** |
| **Version** | **V2.2** |
| **Request for Biological samples and Primary Research Data**  | **Implementation Date:** | **15/02/2017** |

**CONDUCTING RESEARCH USING DATA FROM THE SINGAPORE POPULATION HEALTH STUDIES (SPHS)**

Various investigators will use SPHS datasets for statistical analyses and writing of research articles resulting in a need to check potential overlap between analyses, assure quality control, and ensure that results presented in articles can be independently replicated. Therefore, the following steps have to be followed for use of these data:

1. Complete the data request form and a data analysis proposal (see Annex A). All completed forms are to be submitted to Data Management Section, Saw Swee Hock School of Public Health (SSHSPH) at SSHSPHDataRequest@nus.edu.sg. Subsequently:

a) A reference number will be assigned to the proposal which will then be reviewed by the SPHS Scientific Committee. Members of this committee are:

* Assoc. Prof Jeannette Lee
* Assoc. Prof Rob van Dam
* Prof Tai E-Shyong
* Assoc. Prof Teo Yik Ying (For Genetics Studies)

b) Once the analysis proposal is approved, the database manager will write to the requestor and initiate the provision of relevant data

2. The proposer will conduct the analysis and write the manuscript. Updates may be requested by the SPHS Scientific Committee.

3. After the manuscript has been completed and approved by the co-authors, but before submission to a journal:

1. Have a co-author (generally the second author) conduct a technical review of the manuscript (see Annex B).
2. Preferably, have an independent person check the code of your statistical program. At least, provide descriptions in your code that clarify the different steps of the analysis to an independent investigator.
3. Submit to the database manager:
* The manuscript submission form (see Annex C)
* The submitted manuscript
* The statistical program code

**REQUEST FORM FOR BIOLOGICAL SAMPLES AND RESEARCH DATA**

**Definitions**

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| ***tERMS*** | ***Description*** |
| Data Request | A formal application to request for Research Data and Biological Sample maintained by Saw Swee Hock School of Public Health (SSHSPH) |
| Requestor | The investigator who puts up a Data Request to SSHSPH and is responsible for the use of the Research Data and/or Biological Sample by his/her investigator team in accordance with the terms and conditions set out in this document. |
| Research Data | Refers to the data collected, both identified and de-identified, by researchers of the SPHS. The data can be quantitative or qualitative in nature. |
| Biological Sample | Refers to any blood, urine or DNA sample |
| Provider | SSHSPH and its designated service or third party providers who provide the Research Data or Biological Sample to the Requestor. |

**Instructions**

1. All fields in this form are mandatory. Enter “N.A.” for field that is not applicable.
2. Any add-on request or changes made to previously submitted request must resubmit as amended request. However, the SPHS Scientific Committee and Dean, SSHSPH reserves the final right to ask the requestor to put up a new application if required.

**Requirements for requests for biological samples and primary research data**

The following requirements must be met by the requestor for data and biological sample requests:

1. Obtainethics approval from the institutional review board (IRB) and submit the IRB approval letter and all protocol amendment approval letter(s) that list the approved documents and the approved IRB application which describes the research methodology/protocol.
2. Submit a Data Analysis Proposal (see Annex A)
3. Agree to submit an update on the progress of analyzing the data or biological samples if requested by the SPHS Scientific Committee with effect from the date of delivery of the data or samples
4. Agree to conduct a technical review of the manuscript (see Annex B) and submit the manuscript to be reviewed by at least one member of the SPHS Scientific Committee before publication
5. Agree to include at least one member of the SPHS Scientific Committee as co-author in the manuscript
6. Agree to appropriately cite the Singapore Population Health Studies and its funding sources in the manuscript
7. Agree to fill out the manuscript submission form and submit a copy of the submitted manuscript and analyses codes

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| **Section A: Basic Information of Requestor** |
| 1. Date of Request: (DD/MM/YYYY)
 |  |
| 1. Full Name:
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| 1. Organisation:
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| 1. Role/Designation:
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| 1. Phone Number:
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| 1. Email Address:
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| **Section B: Details of Research Data and Biological Samples** |
| 1. Title of your research study:
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| 1. IRB approval obtained?

*(If obtained, indicate IRB Approval Reference Number and attach a copy of the IRB approval letter and all protocol amendment approval letter(s) that list the approved documents and the latest approved IRB application which describes the research methodology/protocol.)*☐ No ☐ Yes, IRB Approval Reference Number: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |
| 1. Requested Delivery Date (DD/MM/YYYY):

(Kindly note that the date entered should have a minimum of 6 working weeks interval from the date of request, excluding weekends and public holidays) |
| 1. Type of Request (Tick all boxes that are relevant)

☐ : Biological Samples☐ : Research Data - Record-level (Specified Non-identifiable data for each individual) ☐ : Research Data - Record-level (Specified Identifiable data for each individual) ☐ : Research Data - Aggregate-level ☐ : Others, please specify:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | Remarks (if any): |
| 1. Does this request relate to any previous Research Data and/or Biological Samples that you have requested from us?

☐ No, this is a first request/this has no connection with previous request(s).☐ Yes, please state request form reference number and specify how they are related: |
| 1. State the measures you will undertake to ensure the security of the data you have requested for.
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| 1. Please confirm the nature of your request (e.g. for research or operational use). Note that data provided should only be used for the stated request
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| **C: Biological Samples Information** |
| Fill in the table below for the criteria of samples retrieval

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| **Type of Samples (Place a tick against the type of your biological sample request)** | **Fasting status (Only applicable for blood samples: Yes, No or NA)** | **Number of samples (subjects)** | **Volume (ml) per subject (if applicable)** | **Other specifications (e.g. DNA concentration)** | **Tests that will be performed on the samples** |
| □ DNA |  |  |  |  |  |
| □ EDTA Plasma |  |  |  |  |  |
| □ Citrate Plasma |  |  |  |  |  |
| □ Serum |  |  |  |  |  |
| □ RBC |  |  |  |  |  |
| □ Whole blood |  |  |  |  |  |
| □ PBMC |  |  |  |  |  |
| □ Clot |  |  |  |  |  |
| □ Urine (buffered) |  |  |  |  |  |
| □ Urine (neat) |  |  |  |  |  |

1. Describe how the samples obtained will be stored.

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| **D: Acknowledgment** |
| TERMS OF SERVICEThe Requestor is responsible for ensuring that the packaging of Biological Samples for collection from Provider’s facility and the transportation of the Biological Samples must minimally meet local transport regulations stipulated under the Biological Agents and Toxin Act. Provider will not be responsible or accept liability for Biological Samples lost, damaged or compromised in transit from Provider to Recipient. NO LIABILITY FOR USE OF MATERIAL, AND INDEMNITYRequestor hereby undertakes to indemnify, defend and hold harmless Provider, its employees, officers and directors from and against all claims, costs, damages, losses, liability and expenses (including, but not limited to reasonable legal fee) sustained or incurred by Provider or any of its employees or Affiliates directly or indirectly as a result of any claim or action brought against Provider by a third party as a result of Requestor’s actions and/or omissions (including but not limited to any allegation of infringement of property rights in the Research Data or Biological Samples) or the breach of any applicable laws and regulations in relation to the Research Data or Biological Samples by the Requestor. The term “Affiliates” with regards to NUS shall include National University Health System Pte. Ltd. and its respective employees, officers and professional and legal advisors. Except to the extent prohibited by law, the Requestor assumes all liability which may arise from its use, storage or disposal of the Research Data or Biological Samples.ACKNOWLEDGMENTI hereby acknowledge that I am able to fulfill **all** the requirements as stated in this request form and **all** information provided is accurate. In addition, I recognise that in the event that my application has been approved, it is my obligation to keep the received data or biological samples secure and confidential. I will not disseminate any data or biological samples to another third party and hereby agree to use the data or biological samples solely for research purpose as stated in this request form. |
| \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Name of Requestor |  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Signature of Requestor | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Date |

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| ***For Official Use*** |
| ***Request No:*** |  |
| ***Received Date:*** |  |

**ANNEX A. DATA ANALYSIS PROPOSAL**

To be submitted to Data Management Section, Saw Swee Hock School of Public Health (SSHSPH) at SSHSPHDataRequest@nus.edu.sg. An example of an analysis proposal is provided in Annex D.

**Reference and date:** (to be assigned by Data Management Section)

The analysis proposal is about 2-3 pages consisting of the following:

1. Title
2. Proposed authors (can be alphabetical) but should identify first author and senior author
3. Research questions
4. Brief scientific background (~200 words)
5. Study design
6. Study population
	1. Eligible population
	2. Exclusions
7. Outcome variables
8. Exposure variables
9. Covariables
10. Potential confounders considered
11. Potential mediators
12. Potential effect modifiers
13. Statistical analyses
14. Primary analyses
15. Secondary analyses
16. Please list the data source and all the data variables (as according to the data dictionary) which you wish to request for this proposal here:

**ANNEX B. TECHNICAL REVIEW**

For quality control, we request the conduct of a technical review.

The purpose of the technical review is to have a second person look at all of the data presented in the manuscript tables and text, checking for consistency and plausibility.

Examples include:

* Do the numbers in the tables and for the exclusions add up?
* Are the ranges of variables consistent with other publications using SP2 data?
* Are the numbers cited in the text the same as those presented in the Table and the Abstract?
* Do the table / figure numbers in the text refer to the right table/ figure and do the reference numbers in the text refer to the right citation.
* Was the output from the statistical programs accurately copied into the tables and text.

The technical reviewer must be a co-author other than the first author or person who did the computer analyses. Usually, the second author is assigned the responsibility of doing the technical review.

**ANNEX C. MANUSCRIPT SUBMISSION FORM**

To be submitted to Data Management Section, Saw Swee Hock School of Public Health (SSHSPH) at SSHSPHDataRequest@nus.edu.sg

1. Manuscript title:

2. Authors:

3. Corresponding author:

3. Reference number (provided when analysis plan is approved):

4. Version and date of SPHS dataset used:

5. Journal to be submitted to:

Provide files with:

1) The submitted manuscript

2) The statistical program code

**annex D. EXAMPLE OF A DATA ANALYSIS PROPOSAL**

**Can body fat distribution, adiponectin and C-reactive protein explain ethnic differences in insulin resistance?**

**First author:** Gao He

**Proposed co-authors (alphabetical):** Jeannette Lee, Rob M. van Dam, Salome A. Rebello, Tai E Shyong

**Research question:** In an Asian context, we will use path analysis to evaluate to what extent body fatness, adiponectin levels, C-reactive protein and their interconnections mediate the relation between ethnicity and insulin resistance.

**Background:**

South Asians have long been identified in the comparison with Europeans to have a higher risk of insulin resistance [1]; however, so far there is no study that has examined the difference in insulin resistance between ethnic groups in Asia and potential mediators of the relation between ethnicity and insulin resistance. Body fatness and body fat distribution as well as adipokines and inflammation may contribute to ethnic differences in insulin resistance.

Adiponectin level has been shown to be inversely related to risk of type 2 diabetes across diverse populations [2] and it has a protective role against insulin resistance [3]. There is evidence that South Asians have lower adiponectin level than Europeans [4]. In addition, there is a positive association between state of inflammation and insulin resistance and South Asians have been shown to have significantly higher CRP levels than do Europeans [5,6].

**Study Design:** Cross-sectional study

**Study population:**

Eligible population: Singapore prospective study program (SP2)

Exclusion criteria:

* people with diabetes
* people with cardiovascular diseases
* people of other ethnicity than Chinese, Malay and Indian
* people with missing data for the key variables involved in the analysis

**Outcome variables:** Insulin resistance by HOMA-IR

**Exposure variables:** Ethnicity (Chinese, Malay, Indian)

**Covariables:**

* **Potential confounders**
* Age (years)
* Sex (male=1, female=0)
* Smoking status (non-, ex-, light smokers, heavy smokers)
Physical activity (kcal/day)
Alcohol consumption (non-drinker, light drinker, heavy drinker)
* **Potential intermediates:**[Body fatness measurements]

 BMI (kg/m2) derived from height and weight
 Waist circumference (cm)

 Hip circumference (cm)

 Waist-hip ratio

[Adipokines]

 Total adiponectin level (ug/ml)

 High molecular weight adiponectin level (ug/ml)
 HMW adiponectin/Total adiponectin ratio

[Inflammation marker]

 C-reactive protein level (mg/l)

**Statistical analyses:**

* 1. Examine the distribution of each continuous variable by histogram, log-transform those with skewed distribution
	2. Tabulation of baseline characteristics across 3 ethnic groups using proportions for categorical variables, means/geometric means and standard deviation for continuous variables
	3. ANOVA and/or pair-wise ethnic comparison of the characteristics between ethnic groups with necessary adjustment for multiple comparison
	4. As a preliminary step, validate literature-suggested bivariate relationships among variables by correlations(Pearson’s r, Spearman’s r), pay close attention to those highly correlated; and then use multiple linear regression analysis to see whether the effect of a proximal variable on a distal variable is mediated by a mediator
	5. Integrate previous findings and theoretical rationales into a tentative model and conduct path analysis using Pathreg package in STATA for each path to get path coefficients(standardized regression coefficients/beta weights)
	6. Refine the model by dropping paths with non-significant path coefficients and compare it with our hypothetic model
	7. Run path analysis on the refined model and examine the path coefficients to conclude the mediating effects and potential causal relationship

**References**

1. McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *Lancet*. 1991;337:382-386.

2. Li S, Shin HJ, Ding EL, van Dam RM. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2009;302:179-188.

3. Garaulet M, Hernández-Morante JJ, de Heredia FP, Tébar FJ. Adiponectin, the controversial hormone. *Public Health Nutr*. 2007;10:1145-1150.

4. Martin M, Palaniappan LP, Kwan AC, Reaven GM, Reaven PD. Ethnic differences in the relationship between adiponectin and insulin sensitivity in South Asian and Caucasian women. *Diabetes Care*. 2008;31:798-801.

5. Misra A. C-reactive protein in young individuals: problems and implications for Asian Indians. *Nutrition*. 2004;20:478-481.

6. Chambers JC, Kooner JS. Diabetes, insulin resistance and vascular disease among Indian Asians and Europeans. *Semin Vasc Med*. 2002;2:199-214.