October 20th, 2011

THE NORWEGIAN INFLUENZA COHORT STUDY, NorFlu
TERMS AND CONDITIONS FOR ACCESS TO DATA AND BIOLOGICAL MATERIALS

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ABBREVIATIONS

BM	Biological materials
MBRN	Medical Birth Registry of Norway
NorFlu	The Norwegian Influenza Cohort Study
PanFlu SMG	PanFlu Scientific Management Group
NIPH	Norwegian Institute of Public Health
PI	Principal Investigator (for a Sub-study)
REK	Regional Committee for Medical and Health Research Ethics (Norwegian equivalent of institutional review board)
MSIS	The Reporting System for Infectious Diseases
SYSVAK	The Norwegian Immunization Registry

DEFINITIONS

NorFlu Conditions	These NorFlu terms and conditions for access to and use of the NorFlu data and BM.
NorFlu Data	NorFlu questionnaire and data generated through NorFlu Sub-studies included results from analysis of BM (data generated through Sub-studies become NorFlu data after the expiry of the Collaboration Agreement; see below).
Sub-study	Research project making use of NorFlu data and/or biological materials.

Sub-study Institution	Research institution that has applied for and has been granted rights from NIPH to use NorFlu data and BM, subject to its compliance with relevant rules and regulations and the NorFlu conditions for a NorFlu Sub-study, and with which the PI is affiliated.
Collaboration Agreement	Agreement regulating the execution of a Sub-study; signed by the NIPH and the Sub-study institution.
NorFlu Data Centre	The NorFlu data management centre in Bergen, Norway (co-located with MBRN).
De-identified NorFlu data file	Encrypted NorFlu data file in which the linkage to subject identities is retained at the NorFlu Data Centre.
Invention	Any and all inventions, discoveries or know-how, whether or not patentable, conceived or first reduced to practice, based on analyses of NorFlu data and biological materials.
Know-how	Any and all tangible and intangible information, analytical and scientific results and/or data, clinical assessment data, methods, ideas, and any other information arising from analyses of NorFlu data and biological materials.
Study Results	Any and all results of a Sub-study performed in accordance with the Sub-study protocol and the Collaboration Agreement.
Patent Rights	Any and all (a) patents, (b) patent applications, including, without limitation, all provisional applications, substitutions, continuations, continuations-in-part, divisions, reneals, and all patents granted thereon, (c) all patents-of-addition, reissues, re-examinations and extensions or restorations by existing or future extension or restoration mechanisms, including, without limitation, patent term adjustments, patent term extensions, supplementary protection certificates or the equivalent thereof, and (d) any other form of government-issued right substantially similar to any of the foregoing.

RELATED DOCUMENTS

1. NorFlu study protocol	NorFlu study protocol , last revised February 12th 2010 is posted on the NIPH website, www.fhi.no/norflu
2. NIPH application form	S601BE – NIPH application form for access to data and biological materials (www.fhi.no/norflu). NIPH reserves the right to amend the application form at any time
3. NorFlu charges	Charges for NorFlu data and biological materials is available on request (dataaccess@fhi.no). NIPH reserves the right to adjust prices at any time.
4. Return of BM analyses results	NorFlu instructions for return of results of analyses of BM to the NorFlu Data Centre (to be completed).

1. PURPOSE OF CONDITIONS

The NorFlu study was initiated by the Norwegian Institute of Public Health as a part of the follow- up and evaluation after the influenza A (H1N1) pandemic 2009-2010. Accordingly, a number of research questions have been reserved for this purpose to researchers at the NIPH and collaborating partners. Access to data will be provided for other researchers according to the decision of the PanFlu SMG. The purpose of the NorFlu Conditions is to provide the framework for access to and use of NorFlu data and BM, which will facilitate high-quality research based on NorFlu.

2. APPLICANT REQUIREMENTS

The PI must have a PhD, or research experience comparable to a PhD. The PI must also be affiliated with the Sub-study Institution. In order to qualify as a Sub-study Institution, a research institution must document that it has the infrastructure required to conduct research of high quality and to ensure that NorFlu Data and BM are stored securely and in accordance with Norwegian law and regulatory requirements. Institutions applying from outside of Norway must have one or more Norwegian collaborators.

3. APPLICATION PROCESS

The exact contents of the NorFlu database and the NorFlu biobank are described in the NorFlu study protocol (*www.fhi.no/norflu*). Applications are submitted using the standardized NIPH application form (S601BE) which is available on the NIPH website, www.fhi.no. The application form and the mandatory attachments can be submitted electronically to the designated e-mail address: dataaccess@fhi.no.

Applications are evaluated by the PanFlu SMG, which is appointed by the NIPH Director General**.** Applications will be processed within three months after receipt of the application, provided that the application contains sufficient information and all mandatory attachments. If clarifications or supplementary information are required, handling time may be longer.

4. APPLICATION CONTENT

All submitted documents must be written in English. In addition to the completed application form, the following are required:

a. A Sub-study protocol: The Sub-study protocol must include a clear specification of research questions and scientific aims and should state the main exposure and outcome variables as well as other covariates/ confounders. If additional collections of data and BM are planned, or if the Sub-study requires additional contact with NorFlu participants, these plans must be described in detail. Requests for linkages to other health registries must also be specified.
b. Preliminary titles of planned publications.
c. CV for the PI
d. Confirmation of funding, if obtained.
e. Copies of regulatory approvals, if obtained.
f. Other supplementary information necessary for the evaluation of the proposal.

5. EVALUATION OF APPLICATION

The PanFlu SMG evaluates the application based on the following:

a. Scientific quality, originality and feasibility.
b. The purpose of the study should be adherent to NorFlu's main objective and related to diseases primarily associated with influenza related exposures in pregnancy.
c. Scientific merits of the PI and the research group.

d. The potential benefit to preventive or curative medicine.
e. Conflict with other Sub-studies or the interests of collaborators

Sub-studies that require additional collections of data or BM must fall within NorFlu's objectives to find causes of diseases, detect early signs of diseases and describe the development of diseases *primarily associated with exposure to influenza, vaccination or antiviral medication in pregnancy*. There is a high threshold for approval of such Sub-studies. Additional collections will not be allowed if there is any reason to suspect that the additional burden on the participants may jeopardize future follow-up. All costs and expenses for additional collections must be covered by the applicant. Sub-studies with independent collections of data and BM require separate information brochures and consent forms, which must be approved by the PanFlu SMG prior to submission of applications to the REK and other regulatory bodies.

If the PanFlu SMG, after a good faith determination, finds that an application is in conflict with one or more already approved and ongoing NorFlu Sub-studies, the application must be rewritten to eliminate any conflict. The PanFlu SMG will provide the NIPH template (once this is available) for Collaboration Agreements between the Sub-study institution and the NIPH for the particular Sub-study.

Appeals against a rejection of an application must be submitted to the Director General of the NIPH.

6. NorFlu COLLABORATION AGREEMENT

Once the PI has documented that the Sub-study has obtained the necessary funding and regulatory approvals, and the PanFlu SMG has approved the application for the Sub-study, the PanFlu SMG will provide the NIPH template (once this is available) for a Collaboration Agreement between the Sub-study Institution and NIPH. The Collaboration Agreement must be signed by NIPH, the PI and the Sub-study Institution. During the term of the Collaboration Agreement, the Sub-study will be considered ongoing, while after expiry of the Collaboration Agreement, the Sub-study will be considered finalized. This has implications for the rights to NorFlu data and BM (*Sections 8, 9, 13, 15*).

NorFlu will provide the PI of the Sub-study with the data and BM for use during the term of the Collaboration Agreement. The standard duration of an agreement is three years running from the time of signing the agreement, but other time intervals may be chosen, depending on the nature of the Sub-study. Data or biological material should be provided as quickly as possible after the Collaboration Agreement is signed. Once the study has started the PanFlu SMG should be informed. If an extension of the agreement is required, an application must be sent to the PanFlu SMG prior to the expiry date of the original Collaboration Agreement.

The PanFlu SMG must be informed of any significant changes proposed to the Sub-study during the Collaboration Agreement period, and any changes must be approved by the PanFlu SMG prior to the submission of any publications. If suggested changes are approved by the PanFlu SMG, the Collaboration Agreement will be revised accordingly.

Once the Collaboration Agreement is signed, the Sub-study title, name of PI, Sub-study Institution, a summary written for the general public and keywords obtained from the application form will be posted on the NIPH's website, www.fhi.no.

7. STUDY OPTION

PIs are encouraged to submit their applications to the PanFlu SMG as early as possible, in order to facilitate coordination between Sub-studies. If funding and/or regulatory approvals

are pending, the PanFlu SMG can issue an option to the applicant institution. An option is usually issued for one year at a time. During this time, NIPH will inform the applicant of any other proposals that may overlap with the Sub-study. As a rule, the first applicant will have priority; however, the commitment is not legally binding to NIPH. Until a Collaboration Agreement is signed, the NIPH reserves the right to adjudicate between different proposals. An option period may be prolonged, upon request to the PanFlu SMG.

If requested, the PanFlu SMG will issue letters of support to applicants to whom options have been granted. Such letters may be used to support applications for funding or regulatory approvals. Letters of support are not legally binding to NIPH.

8. NorFlu DATA

The content of the NorFlu database is described in detail in NorFlu study protocol. The following types of data are available:

a. NorFlu questionnaire data: Access requires approval from the PanFlu SMG.

b. MBRN data for NorFlu participants: Access requires approval from the PanFlu SMG.

c. Linkage to data from national health registries: Access requires approval from PanFlu SMG and data owners of the national health registry in question.

d. Data collected or generated by NorFlu Sub-studies: For ongoing Sub-studies, access requires approval from the PI or steering committee of the Sub-study of interest. For finalized Sub-studies, the data are governed in the same manner as other NorFlu data, and access requires approval from the PanFlu SMG only.

Research files containing the variables listed in the Collaboration Agreement will be submitted from the NorFlu Data Centre to the PI. The PI will distribute the file to the scientific collaborators approved for data access. As a rule, the data files will be de-identified.

The MBRN data are linked to the pregnancy questionnaires for each woman. The NorFlu questionnaire data will be updated as new questionnaires are available. The files will contain data from the questionnaires that have been specified in the Collaboration Agreement. If the PI wants additional data from questionnaires that will be available in the future, the reason must be stated in the application. This will require a de-identified data file to permit linkage of new information at a later stage. The additional cost of the extra update will be added to the Sub-study charge.

9. NorFlu BIOLOGICAL MATERIALS

The content of the NorFlu biobank is described in detail in the NorFlu study protocol. Access to NorFlu BM is regulated by the PanFlu SMG, under the following limitations/conditions:

a. Access to BM from participants in the NorFlu study should only be provided to studies of scientific significance and originality related to diseases *primarily associated with exposure to influenza, vaccination or antiviral medication in pregnancy*.
b. To prevent early depletion of samples from any given NorFlu participant, specified amounts of BM – from children and mothers alike – should as a precaution remain in the NorFlu biobank until the child reaches certain age points:
    - 600 micro-litres (two wells) of plasma/sera and 930 micro-litres (one well) of DNA must remain until the child reaches eight years of age.
    - 300 micro-litres (one well) of plasma and 100 micro-litres of DNA must remain until the child reaches 18 years of age.

Exceptions from this precaution may be decided by the PanFlu SMG.

c. Access to BM requires approval from the PanFlu SMG.

d. Access to BM from NorFlu participants who are also in the MoBa study (mainly non-pregnant samples) requires approval from the PanFlu SMG. The PanFlu SMG should also inform the MoBa SMG, but no formal approval is required.

e. BM collected through NorFlu Sub-studies: For ongoing Sub-studies, access requires approval from the PI or steering committee of the particular Sub-study. For finalized Sub-studies, the BM is governed in the same manner as ordinary NorFlu BM, and access requires approval from the PanFlu SMG only.

Apart from the above, no exclusive rights to BM are granted. Retrieval is conducted on a first-come-first-serve basis. BM is retrieved and shipped according to the specifications of the Collaboration Agreement.

Results obtained from analyses of BM must be returned to the NorFlu Data Center before linkage to the approved questionnaire data will be performed. Study results should be returned with documentation about analysis done. A merged file with questionnaire data and BM (Results file) will be submitted to the PI.

The result files must be accompanied by a description, in English, of the analysis methods written in a way that makes it easily accessible and ready for use by other researchers. The data will be made available to other Sub-studies at the end of the Sub-study Collaboration Agreement, or earlier if allowed for in the Collaboration Agreement. (The procedures for data return will be provided in a separate document that is under preparation).

10. NorFlu STUDY CHARGES

The charges for use of NorFlu data and BM are available on request (dataaccess@fhi.no). The charges applied will be those that are current as of the effective date of the Collaboration Agreement.

11. REGULATORY APPROVALS

NorFlu was evaluated by the Regional Committee for Medical and Health Research Ethics in Norway (REK) prior to the inception of the study, in 2009 and 2010, reference REK 2009/2165.

All Sub-studies applying for questionnaire data or BM must be approved by the REK. If datafiles or BM is to be transferred abroad for analysis this should be stated in the application to REK.

12. LINKAGE BETWEEN NORFLU AND OTHER HEALTH REGISTRIES

NorFlu data may be linked to other national health registries and to socioeconomic and demographic data from Statistics Norway. Researchers may apply to PanFlu SMG for access to an established linked file. A Sub-study that requires a linkage between NorFlu data and other registries should be within a specific scientific aim and have approval from the REK.

13. NorFlu PUBLICATION POLICY

1. Confounder publication
   The PanFlu SMG has a restrictive policy when it comes to publicizing the direct effects of confounding variables, in order to avoid infringement on other Sub-studies.

Such information should not be published, but may be submitted to referees/editors if required.

2. Administrative review
   All manuscripts should undergo an administrative review by the PanFlu SMG prior to submission. This is not a scientific review, but it ensures that NorFlu is described correctly, that mandatory references are included, and that the analyses are in accordance with the stated scientific aims of the Collaboration Agreement and do not overlap with other NorFlu Sub-studies. NIPH does not take responsibility for the scientific content of the manuscript. NorFlu must be made visible in the methods chapter, and the description of NorFlu must be in accordance with the text suggested below.

3. Checklist for publication
   Publication drafts with completed checklist must be submitted to the PanFlu SMG at the e-mail address dataaccess@fhi.no. NorFlu will send a receipt confirmation. Our goal is to evaluate all papers within two weeks after receipt is confirmed.

4. Syntax
   The manuscript must be accompanied by a syntax file showing how the study population was selected and how the main variables were defined. The syntax will only be used to reproduce the results or to comment on them in a letter to the editor of the journal in which the manuscript is published. Stored syntax files will be treated confidentially, and cannot be distributed to others without a written permit from the Sub-study PI..

5. Media strategy
   Results from Sub-studies should not be made publicly available to newsmedia until they have been published in scientific journals or as printed abstracts at scientific conferences. In all contact with newsmedia, it must be made clear that results are based on NorFlu.

Suggested standard text of NorFlu for use in "Abstract" and "Material and Methods"

In the abstract:

This study is based on the Norwegian Influenza Cohort Study (NorFlu) conducted by the Norwegian Institute of Public Health.

In material and methods:
The Norwegian Influenza Cohort Study (NorFlu) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. Pregnant women were recruited from four hospitals in Norway from February 2010 through September 2010. Participants had their last menstrual period (LMP) between June 1st and December 1st 2009. Three of the hospitals are situated in Eastern Norway (Oslo-area; Oslo University Hospital Ullevål, Oslo University Hospital Rikshospitalet and Vestre Viken Hospital Asker and Bærum), and one in Western Norway (Bergen; Haukeland University Hospital. About 41% of the invited women consented to participate. The cohort includes about 3200 mother and child pairs. Blood samples were obtained from mothers and children (umbilical cord) at birth. About 320 non-pregnant controls were recruited to NorFlu among participants in another large pregnancy cohort study in Norway, the MoBa study.

Follow-up is conducted by questionnaires at regular intervals and by linkage to national health registries. The current study is based on (*description of questionnaires, biological material and registry linkage in the current dataset to be filled in*). The quality-assured data

files were released for research on (*date to be filled in*). Informed consent was obtained from each NorFlu participant upon recruitment. The study was approved by The Regional Committee for Medical Research Ethics in South-Eastern (*or other, if applicable*) Norway.

Acknowledgement: The Norwegian Influenza Cohort Study (NorFlu) is supported by the Norwegian Ministry of Health. We are grateful to all the participating families in Norway for taking part in this ongoing cohort study.

Posters and abstracts do not require approval from the PanFlu SMG, but a copy must still be submitted to the PanFlu SMG for information purposes, at the e-mail address dataaccess@fhi.no.

If there is suspicion of violation of accordance between manuscripts and approved research questions from the Sub-study description the PI or manuscript author will be contacted for clarification. The manuscript then has to be revised to fit with the stated scientific aims. If agreement cannot be achieved, and the matter is considered to breach the Collaboration Agreement, one or more of the following actions will be taken:

- A written notification will be sent to the Sub-study institution informing that the Sub-study has overstepped the agreement of rights to analysis.
- A written notification will be sent to editors of the journals where the manuscript has been submitted, informing them of the situation.
- The Collaboration Agreement will be terminated and further rights of analysis will be withdrawn from the Sub-study.

14. EXPIRY OF COLLABORATION AGREEMENT

As a main rule Sub-study file should be deleted upon expiry of the Collaboration Agreement. The PI is responsible for issuing a statement to the PanFlu SMG confirming that this procedure has been conducted, and the study identifier list will be destroyed at the NorFlu Data Center.

Any remaining BM must be returned to the NorFlu Biobank, unless otherwise decided by the PanFlu SMG.

A written report for the general public at most one page must be submitted to dataaccess@fhi.no. This report will be published on the NorFlu website.

After the expiry of the Collaboration Agreement, the PI no longer has exclusive rights to the scientific aims of the Sub-study. Other researchers may then apply for access to and use of NorFlu data and BM to conduct research within similar or overlapping aims. PI may apply for extended Collaboration Agreement period if needed.

15. OWNERSHIP OF INVENTIONS, KNOW-HOW AND STUDY RESULTS

Inventions, Know-how and Study Results developed on the basis of NorFlu data and BM will be jointly owned by NIPH and the Sub-study Institution.

While the Sub-study is ongoing, the Sub-study Institution must promptly disclose all Inventions in writing, confidentially, to NIPH. NIPH and the Sub-study Institution shall enter into good faith negotiations to form a binding inter-institutional agreement with respect to the rights associated with any Invention, Know-how and Study results. Such inter-institutional agreement also shall regulate the filing of patent applications (if any), and patent prosecution and maintenance, the sharing of costs related to any such activities, as well as the sharing of

income from any commercialization activities associated with products resulting from any such Invention.

Regardless of what the parties may agree upon in an inter-institutional agreement, NIPH shall retain a royalty-free, non-exclusive, worldwide, non-sublicensable, paid-up, perpetual licence to use the Invention and intellectual property arising from the Sub-study for internal, non-commercial purposes.

16. LIMITATION OF LIABILITY

Collaboration Agreements will contain language confirming that the NorFlu data and BM with respect to any Sub-study are provided without any warranty, express or implied. Moreover, NIPH makes no representation or warranty that use of such NorFlu data and BM will not infringe any patent rights or other proprietary rights of a third party.

17. TERMINATION OF COLLABORATION AGREEMENTS

Collaboration Agreements will contain a termination clause regulating the termination of the Collaboration Agreement for cause. Agreements also may include a clause regulating the termination of part of the Collaboration Agreement, for example a project within the Sub-study if a milestone is not achieved. Upon termination of a Collaboration Agreement, the terms concerning consequences upon expiry of such agreements will apply.

18. GOVERNING LAW

Any Collaboration Agreement will be governed by and interpreted, and all rights and obligations of the parties will be determined in accordance with, the laws of Norway. This is important to ensure consistency of the interpretation of the various Collaboration Agreements executed with Sub-study institutions from various jurisdictions.

19. MISCELLANEOUS

Collaboration Agreements will contain other clauses customary for a research Collaboration Agreement.