Norwegian **Mother and Child** Cohort Study

TERMS AND CONDITIONS FOR ACCESS TO DATA AND BIOLOGICAL MATERIALS

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ABBREVIATIONS

ABC	The Autism Birth Cohort Study (case-control study of autism nested within MoBa)
BM	Biological materials
GWAS	Genome-wide association study
MBRN	Medical Birth Registry of Norway
MoBa	The Norwegian Mother and Child Cohort Study
MoBa SMG	MoBa 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)

DEFINITIONS

MoBa Conditions	These MoBa terms and conditions for access to and use of the MoBa data and BM.
MoBa Data	MoBa questionnaire and ultrasound data, and data generated through MoBa Sub-studies included results from analysis of BM (data generated through Sub-studies become MoBa data after the expiry of the Data/Material Transfer Agreement; see below).

Sub-study	Research project making use of MoBa data and/or biological materials.
Sub-study Institution	Research institution that has applied for and has been granted rights from NIPH to use MoBa data and BM, subject to its compliance with relevant rules and regulations and the MoBa conditions for a MoBa Sub-study, and with which the PI is affiliated.
Data/Material Transfer Agreement	Agreement between the NIPH and Sub-study institution regulating the execution of a Sub-study in accordance to the Sub-study application and MoBa Approval Letter.
MoBa Data Center	The MoBa data management center in Bergen, Norway (co-located with MBRN).
Anonymized MoBa data file	Encrypted MoBa data file in which the linkage to subject identities has been erased.
De-identified MoBa data file	Encrypted MoBa data file in which the linkage to subject identities is retained at the MoBa Data Center.
Invention	Any and all inventions, discoveries or know-how, whether or not patentable, conceived or first reduced to practice, based on analyses of MoBa 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 MoBa data and biological materials.
Study Results	Any and all results of a Sub-study performed in accordance with the Sub-study protocol and the Data/Material Transfer Agreement.
Patent Rights	Any and all (a) patents, (b) patent applications, including, without limitation, all provisional applications, substitutions, continuations, continuations-in-part, divisions, renewals, 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. MoBa study protocol	MoBa study protocol I, last revised December 2005, and the end of inclusion protocol II of October 2012 is posted on the NIPH website, www.fhi.no/moba-en
2. NIPH application form	S601BE – NIPH application form for access to data and biological materials (www.fhi.no/moba-en). NIPH reserves the right to amend the application form at any time

3. MoBa charges	Charges for MoBa data and biological materials. The price list is posted on the NIPH website, www.fhi.no/moba-en. Prices are adjusted at regular intervals (*Section 9*). NIPH reserves the right to adjust prices at any time.
4. Return of BM analyses results	MoBa instructions for return of results of analyses of BM to the MoBa Data Center (to be completed).

1. PURPOSE OF CONDITIONS

The purpose of the MoBa Conditions is to provide the framework for access to and use of MoBa data and BM, which will facilitate high-quality research based on MoBa.

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 MoBa Data and BM are stored securely and in accordance with Norwegian law and regulatory requirements. If sub-studies explore objectives were NIPH have been assigned national obligations, or have experienced researchers within the study aim in question, MoBa may suggest that a co-investigator from NIPH is included in the sub-study. Institutions applying from outside of Norway must have one or more Norwegian collaborators.

3. APPLICATION PROCESS

The exact contents of the MoBa database and the MoBa biobank are described in the MoBa study protocol (*Attachment 1*). Applications are submitted using the standardized NIPH application form (S601BE) (*Attachment 2*), 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 MoBa SMG, which is appointed by the NIPH Director General. There are approximately six application deadlines per year, which are posted on the NIPH website. Applications will be processed within two months of the preceding deadline, 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. Sub-study protocol: The Sub-study protocol must include a clear specification of research questions and scientific aims. If additional collections of data and BM are planned, or if the Sub-study requires additional contact with MoBa participants, these plans must be described in detail. Requests for linkages to other health registries must also be specified.
b. Preliminary titles of 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 MoBa SMG evaluates the application based on the following:

a. Scientific quality, originality and feasibility.
b. Scientific merits of the PI and the research group.
c. The potential benefit to preventive or curative medicine.
d. Conflict with other Sub-studies or the interests of collaborators

Sub-studies that require additional collections of data and BM must fall within MoBa's objectives to find causes of diseases detect early signs of diseases and describe the development of diseases. There is a high threshold for approval of such Sub-studies. Researchers who want to establish a sub-cohort in MoBa should contact the MoBa administration at an early stage of planning the study. A close cooperation between the researchers and the MoBa administration is important from the start to assure that all technical issues are taken into consideration. Additional data 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 MoBa SMG prior to submission of applications to the REK and other regulatory bodies. All results from biological material and additional data that are collected in MoBa sub-studies should be made available for other researchers by end of the Data/Material Transfer Agreement period.

If the MoBa SMG, after a good faith determination, finds that an application is in conflict with one or more already approved and ongoing MoBa Sub-studies, the application must be rewritten to eliminate any conflict. Alternatively, the applicant may establish a scientific collaboration with the Sub-study Institution for the ongoing Sub-study. The applicant is responsible for executing such collaborations.

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

6. MoBa APPROVAL LETTER AND DATA/MATERIAL TRANSFER AGREEMENT

Once the PI has documented that the Sub-study has obtained the necessary funding and regulatory approvals, and the MoBa SMG has approved the application for the Sub-study, the MoBa SMG will issue an Approval Letter. The Approval Letter will together with the application form the basis of the Data/Material Transfer Agreement.

According to the term of the Material Transfer Agreement, the Sub-study has permission to analyse the BM on behalf of MoBa. This has implications for the rights to MoBa BM. (*Sections 8, 9, 13, 15*).

MoBa will provide the PI of the Sub-study with the data and BM for use according to the term of the Data/Material Transfer Agreement. By receiving MoBa data and BM the PI of the Sub-study is committed to comply with the terms and condition of MoBa. The standard duration of an approval is three years, but other time intervals may be chosen, depending on the nature of the Sub-study. If an extension of the approval is required, an application must be sent to the MoBa SMG prior to the expiry date of the original Data/Material Transfer Agreement.

The MoBa SMG must be informed of any significant changes proposed to the Sub-study during the Data/Material Transfer Agreement period, and any changes must be approved by the MoBa SMG prior to the submission of any publications.

Once the Approval Letter is issued, 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 MoBa SMG as early as possible, in order to facilitate coordination between Sub-studies. If funding and/or regulatory approvals are pending, the MoBa 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 an Approval Letter is received the NIPH reserves the right to adjudicate between different proposals. An option period may be prolonged, upon request to the MoBa SMG.

If requested, the MoBa 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. MoBa DATA

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

a. MoBa questionnaire data: Access requires approval from the MoBa SMG.

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

c. MoBa ultrasound data: Access requires approval from the MoBa SMG

d. Data collected or generated by MoBa 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 MoBa data, and access requires approval from the MoBa SMG only.

Research files containing the variables necessary to answer the research questions, listed in the Approval Letter, will be submitted from the MoBa Data Center to the PI. The PI will distribute the research file to the scientific collaborators approved for data access. As a rule, the data files will be anonymized. In some cases, de-identified data files are required to link data from different Sub-studies, to update research files during the course of the Sub-study, or to merge results of BM analyses with other MoBa data. Requests for such de-identified files must be specified in the application.

MoBa questionnaire data and MBRN data are updated annually. The research file will contain data from the last updated source files, unless otherwise specified in the Approval Letter. If the PI wants data that are updated more recently than the last regular update, the reason must be stated in the application. The additional cost of the extra update will be added to the Sub-study charge.

9. MoBa BIOLOGICAL MATERIALS

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

a. To prevent early depletion of samples from any given MoBa participant, specified amounts of BM – from children and parents alike – must remain in the MoBa biobank until the child reaches certain age points:
   - 900 micro-litres (three wells) of plasma 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.

b. The collection of the K1 environmental samples (whole blood, plasma, urine) from mothers during pregnancy was partly funded by the NIEHS. K1 environmental samples collected in or after 2002 are reserved for joint utilization by NIPH and NIEHS, for use in Sub-studies in which both NIPH and NIEHS are collaborators. Use of the samples requires approval from both institutions.

c. Access to RNA samples requires approval from the MoBa SMG and the ABC Steering Committee, since ABC study collaborators have contributed funding specifically for the collection of RNA samples.

d. BM from participants in the ABC study is reserved for use by ABC study collaborators. Use of the samples requires approval from both the MoBa SMG and the ABC Steering Committee.

e. BM from some restricted groups, e.g. twin children, can only be included as control population in Sub-studies after a scientific consideration by the MoBa SMG.

f. Access to milk teeth in MoBa requires approval from the MoBa SMG and the MoBaTann Steering Committee. The dental department of the University of Bergen is responsible for the milk teeth biobank, and has contributed to funding the collection of milk teeth.

g. BM collected through MoBa 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 are governed in the same manner as ordinary MoBa BM, and access requires approval from the MoBa SMG only.

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

Results obtained from analyses of BM must be returned to the MoBa 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.
Three years after the analyses results are sent to the MoBa Data Center they will be made available to other Sub-studies. Researchers may apply for prolonged exclusive rights to the analytical data within a scientific aim.
For a time period of three years, after the analytical data are made available for new sub-studies, the research group conducting the BM analyses will be offered collaboration in sub-studies using their data.

10. MoBa STUDY CHARGES

The current charges for use of MoBa data and BM are provided in the price list posted on the NIPH website, www.fhi.no/moba-en. The charges applied will be those that are current as of the effective date of the Agreement Letter.

11. REGULATORY APPROVALS AND LINKAGES TO OTHER REGISTERIES

MoBa is regulated by the Norwegian Data Inspectorate. The current license was obtained in April 2012. It is only valid for a limited amount of time, since the legislation regulating health registries and large-scale epidemiological studies is currently undergoing change. A permanent license will be obtained once the legislative changes are implemented. MoBa was also evaluated by the REK prior to the inception of the study, in 1996 and 1998.

MoBa questionnaire data files that are anonymous may be obtained without an approval from the REK.

Sub-studies that use de-identified MoBa questionnaire data files will need an approval from the REK.

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

12. LINKAGE BETWEEN MOBA AND OTHER HEALTH REGISTRIES

MoBa data may be linked to other national health registries and to socioeconomic and demographic data from Statistics Norway. A Sub-study that requires a linkage between MoBa data and other registries should be within a specific scientific aim and have approval from the REK. The linkage also requires approval from the MoBa SMG and the owner of the relevant health registry. The applicant is responsible for executing and funding new linkages. Other researchers may apply to MoBa SMG for access to an established linked file.
MoBa has obtained an approval for linkage to the Medical Birth Registry of Norway (MBRN) regarding the birth of the MoBa child. Information from MRBN about siblings or parents birth will require a separate approval.

13. MoBa PUBLICATION POLICY

The MoBa 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.

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

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

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.

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 MoBa.

Suggested standard text and references:

Abstract: This study is based on the Norwegian Mother and Child Cohort Study (MoBa).
Material and methods: The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health (1-3). Participants were recruited from all over Norway from 1999-2008. The women consented to participation in 40.6% of the pregnancies. The cohort now includes 114.500 children, 95.200 mothers and 75.200 fathers.

If blood samples were used in the current study
Blood samples were obtained from both parents during pregnancy and from mothers and children (umbilical cord) at birth.
MoBa has obtained a licence from the Norwegian Data Inspectorate.
The current study is based on version (*to be filled in*) of the quality-assured data files released for research on (*to be filled in*). The current study was approved by The Regional Committee for Medical Research Ethics.

Acknowledgement: The Norwegian Mother and Child Cohort Study is supported by the Norwegian Ministry of Health, and the Ministry of Education and Research, NIH/NIEHS (contract no N01-ES 75558), NIH/NINDS (grant no.1 UO1 NS 047537-01, grant no 2 UO1 NS 047537-06A1). We are grateful to all the participating families in Norway who took part in this ongoing cohort study.

References:

1. *Mandatory:* Magnus P, Irgens LM, Haug K, Nystad W, Skjaerven R, Stoltenberg C and the MoBa Study Group. Cohort profile: The Norwegian Mother and Child Cohort Study (MoBa). Int J Epidemiol 2006;35:1146-50.
2. *If biological material is used:* Rønningen KS, Paltiel L, Meltzer HM, Nordhagen R, Lie KK, Hovengen R, Haugen M, Nystad W, Magnus P, Hoppin JA. The biobank of the Norwegian mother and child cohort study. Eur J Epidemiol 2006;21:619-25.
3. *If relevant:* Nilsen RM, Vollset SE, Gjessing HK, Skjærven R, Melve KK, Schreuder P, Alsaker ER, Haug K, Daltveit AK, Magnus P. Self-selection and bias in a large prospective pregnancy cohort in Norway. Paediatr Perinat Epidemiol 2009; 23: 597-608.

Scientific credit should be provided to the MoBa Cohort and NIPH. Posters and oral power point presentations should include the logo of MoBa and NIPH. Logo for MoBa and NIPH are available at the web site. You will find more information on www.fhi.no/moba-en under the menu “Researchers and data access”. Posters and abstracts do not require approval from the MoBa SMG, but a copy of the presentation and poster should be submitted to the MoBa 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 Data/Material Transfer 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 Data/Material Transfer Agreement will be terminated and further rights of analysis will be withdrawn from the Sub-study.

14. EXPIRY OF DATA/MATERIAL TRANSFER AGREEMENT

As a main rule Sub-study research file should be deleted upon expiry of the project period. The PI is responsible for issuing a statement to the MoBa SMG confirming that this procedure has been conducted. If the Sub-study research file is de-identified the study identifier list will be destroyed at the MoBa Data Center.

Any remaining BM must be returned to the MoBa Biobank or destroyed.

A written report describing the findings of the Sub-study, at most one page, should be submitted to dataaccess@fhi.no. This report may be published on the MoBa website.

After the expiry of the Data/Material Transfer 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 MoBa data and BM to conduct research within similar or overlapping aims. PI may apply for extended exclusive right period if needed.

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

Inventions, Know-how and Study Results developed on the basis of MoBa 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 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

Data/Material Transfer Agreements will contain language confirming that the MoBa 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 MoBa data and BM will not infringe any patent rights or other proprietary rights of a third party.

17. TERMINATION OF DATA/MATERIAL TRANSFER AGREEMENTS

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

18. GOVERNING LAW

Any Data/Material Transfer 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 Data/Material Transfer Agreements executed with Sub-study institutions from various jurisdictions.

19. MISCELLANEOUS

The Approval Letter and this MoBa conditions document will contain other clauses customary for a research Data/Material Transfer Agreement.