Norwegian **Mother and Child** Cohort Study

Revised PROTOCOL
End of enrolment - Protocol II

December, 2010

Norwegian Institute of Public Health

End of inclusion Protocol II
The Norwegian Mother and Child Cohort Study (MoBa)

Revised December 2010

Table of contents

Summary

The Norwegian Mother and Child Cohort Study (MoBa) was established and is conducted by the Norwegian Institute of Public Health (NIPH). The ideas behind the study were formulated in the early 1990s. MoBa is an ambitious family-oriented cohort study that aims to find causes of diseases and explain trajectories and variability of health-related traits over a life-course span. Between 1999-2008 pregnant women were invited to take part in the study around the time of the ultrasound examination in week 17-20 of gestation. The fathers of the children were also invited to participate. Biological material has been collected from mothers, fathers and children and has been stored in a biobank. Data are collected from regular questionnaires about general health, diet and environmental exposure- analyses of biological material and linkages to information from health registries. The cohort includes approximately 108,000 children, 90,700 women and 71,500 men. MoBa is an open resource for research on an international scale. This protocol describes the data collection, data management and guidelines for the research activities. The previous protocol I, (enrolment) last revised June 2008, is available on www.fhi.no/moba, and gives more detailed information on recruitment and inclusion procedures as well as the collection of data and biological materials. For the period 1999-2009, direct costs have totaled about 200 million Norwegian Kroner. About half of the funding has been supplied by the Ministry of Health and Care Services and the NIPH, and the rest from various funding agencies, in Norway and abroad.

Background

A long list of diseases cannot be prevented due to lack of etiological insight. During the past 150 years, much progress has been made in understanding infections and monogenic diseases, and risk factors for many chronic disorders have been described. However, for the majority of complex diseases, primary prevention is not possible. In this situation, new data sets that support research in a life-course perspective are needed. Data sets with rich information on exposures and outcomes, that include social and biological factors, can be used by researchers in fields with widely different types of causal models. MoBa is designed to answer scientific hypotheses by collecting as much relevant exposure and disease outcome information as possible in order to serve a broad audience of researchers investigating many diseases.

Aims

The main aim of the study is to find causes of diseases. Additional aims are to detect early signs of disease and to describe the development of diseases. A broader discussion of aims and methods is given in Magnus P et al. Cohort profile: The Norwegian Mother and Child Cohort Study. Int J Epidemiol 2006;35:1146-50.

Design

The design is prospective and observational (cohort) and is family-oriented around each pregnancy, including information from the child, father and mother.

Sub-cohorts with additional data collection will be formed within the main cohort. Also, nested case-cohort and case-control designs will be employed, for example when biological material that was collected early is analysed.

Population and sampling

The Norwegian population of pregnant women, their children and their partners form the target population. The actual sampling frame consists of pregnant women who attended the routine ultrasound appointment around week 17-20 of pregnancy in participating Norwegian hospitals. Lists of these women were sent to the central data collection unit of MoBa, and the women received a postal invitation. The final sample consisted of women and their partners who gave a written consent to participate (about 38,5% response). The sampling was to some extent opportunistic, depending on available funding and the participation of local hospitals at various times during the recruitment period (1999-2008). Thus, in the beginning only a small proportion of the pregnant population was approached. The recruitment began in the county of Hordaland in Western Norway in 1999, and expanded gradually. Fathers were included from 2000. From 2005 it became a nationwide study where 50 out of 52 hospitals in Norway participated. Only facilities with more than 100 births per year were targeted. After May 31st, 2008, most of the hospitals ended the recruitment but the eight largest hospitals in Norway continued the recruitment until December 31st, 2008. The last birth into the cohort occurred in June 2009.

The selection to the sample has been described (Nilsen R et al: Self-selection and bias in a large prospective pregnancy cohort in Norway. Paediatr Perinatal Epidemiol 2009;23:596-608), and suggests that although some prevalence estimates are biased, the association measures between exposures and outcomes are not. On the condition that the woman had consented, the participation rate among their partners was about 80%.

The sample size that is available for analysis will differ depending on the type of data needed. Questionnaires are sent to the participants over a long period. Participants who choose not to complete one questionnaire can still remain in the study and be asked to complete the next one. People who decide to withdraw from the cohort will be asked if already collected data and biological specimens may remain as a resource in the database, so that withdrawal will only affect future participation. If this is denied, the data about the person will be deleted and the biological material destroyed. Participants that withdraw from the study will no longer be contacted. As of October 2010 about 2510 of participants have withdrawn form the cohort. Among these, 99 have requested to have all their data deleted.
A sample size of 100 000 participants is needed because many diseases are relatively rare and exposure may be infrequent. A typical congenital abnormality has prevalence at birth of about 1 per 1000, so 100 cases can be expected. However, such malformations are clinically heterogeneous, so it may be desirable to carry out analyses in sub-groups. For some malformations, and for other rare conditions such as childhood cancers, collaboration with other cohorts will be sought.

Table 1 Number of participants in MoBa (October 2010)

	Number	% of invited
Pregnancies	107 008	38.5%
Pregnancies with information from fathers	82 471	31,7%
Children	108 639	
Mothers participating	90 725	
Fathers participating	71 574	
Twin pairs	1 871	
Triplet trios	21	
Mothers participating with more than one child	15 256	

Variables

Exposure variables
An exposure variable is defined as one if it is named in the study aims as a potential causal factor. Many of the questions posed in the questionnaire will either directly or indirectly measure exposure. Similarly, specific blood- and urine factors will be exposure variables when they are analysed as causal factors. A fuller understanding of the framework for these variables can be obtained by examining the content of the questionnaires and the detailed description of blood- and urine sample collection and storage. Some sub-studies will include the collection of further exposure variables.

Outcome variables
An outcome variable is defined as one that describes or defines a health condition, either from the questionnaire, registry or urine- and blood samples. Normally these variables become effect variables in a cause-effect model, but they can also be exposure variables for other health variables. For example a mother's mental health can be the cause of a child's future psychiatric complaint, and low birth weight can lead to a number of childhood ailments. Many outcome variables will be collected from linkages to other health registries or as part of sub-studies.

Confounders and other variables
The questionnaire will also include a number of other variables which conceptually are neither exposure nor health variables. Some of these will be used as confounders in the statistical analyses, while others are included because they are background variables used for more descriptive purposes.

Instrument documentation
To help researchers that are planning to use MoBa data, an overview of instruments and questions used in MoBa study is being written. Such an overview will be provided for each

questionnaire. Each document will contain information about questionnaire forms and revision dates, the aim of each questionnaire, a description of the instruments and the rationale for choosing the instrument. In addition, a suggested syntax will be made available for the most commonly used variables and instruments. A syntax file describes the original file and contains a description of how selection of the study population could be performed. The syntax also suggests how the variables/algorithms can be defined and which scales are suitable for the analyses.

Table 2 Examples of exposures and outcomes to be investigated in the MoBa

Exposures	
Dietary factors	Occupational hazards
Environmental toxins	Medication
Hereditary factors	Personal habits
Infections	Physical activity
Interpersonal relationships	Work situation

Diseases	
Asthma/allergy	Diabetes
Breast cancer	Pelvic pain
Cancer	Premature birth
Congenital malformations	Rheumatism
Depression	Stillbirth

Reliability and validity studies

Definition of important variables and establish of standard syntaxes
A standard definition of key variables (smoking, alcohol use) from the MoBa dataset to ensure that research from the MoBa cohort will have the same point of origin is needed.

Data collection

Questionnaires
A main source for variables is the self-reported information through postal and web-based questionnaires. Questionnaires are sent to the mothers in the month that the child reaches the applicable age. If a completed questionnaire has not been returned to data management within 3 weeks a reminder including a new questionnaire is sent. Before questionnaires are sent, data management ensures that both the child and mother are alive.

All questionnaire forms are available on www.fhi.no/moba

Table 3 MoBa Questionnaires as of October 2010

	Time	Main focus	Number dispatched	Number returned	Response rate
Ultra-sound form	Week 17-20 of pregnancy	Growth of foetus (estimate of gestation age) malformations, numbers of foetus and plancenta position	106 960	87 600	81,9 %
Mother	Pregnancy				
Q1	Wk 13-20 of pregnancy	Previous pregnancy and outcome, medical history before and during pregnancy, medications, occupation, exposures at work and at home, lifestyle, mental health	106 928	101 828	95.2%
Q2	Wk 22	Diet	105 369	97 275	92.3%
Q3	Wk 30	Antenatal care, health changes, work situation, lifestyle	103 745	94 362	91,0%
Mother	Age of child				
Q4	6 month	About the birth, child birth, development and nutrition, maternal health, lifestyle and well-being	105 973	89 821	84.8%
Q5	18 month	Child health, development, behavior, nutrition and daily life, maternal health, lifestyle and well-being	103 540	74 976	72,4%
Q6	36 month	Child health, development, behavior, nutrition and daily life, maternal health, lifestyle and well-being	79 378	47 083	59,3%
Q7	5 y	Neurodevelopmental disorders, language delay			
Q8	7 y	Child health, lifestyle and nutrition			
Q 9	8 y	Psychological behavioral and language skills			
Q10	Children	Influenza and vaccines June 2010	104 560	14 382	13,8%
Q10	Mothers	Influenza and vaccines June 2010	87 200	11 766	13,5%
Father					
QF	Wk 13-17 of pregnancy	Medical history, health, occupation, exposures, lifestyles, nutrition	82 471	77867	94.4%

Biological material

EDTA whole blood from both parents and urine samples from mother were collected during pregnancy, from the child's umbilical cord right after birth, and from the mother post-partum. RNA collection was initiated in 2005, and is available for approximately 45.500 children included in the cohort. In addition, collection of milk teeth from all children at 7 years of age is performed.

All biological samples were sent from the hospitals to the Biobank in Oslo by regular mail. This implies that the samples have been subjected to ambient temperature during transportation. Further, after arrival at the repository, the blood samples may have been stored at room temperature before DNA extraction for a period of several days. However, separation of plasma from the whole blood samples, as well as whole blood storage was performed on the day of arrival. This was also true for the urine samples that were stored on ice from arrival to storage at -80C. For further details of handling and available specimens see appendix 2 Biobank description.

Table 4 MoBa biological sample collections as of October 2010

Sample	Time of collection	Sample type	Number of participants	% received from total participants
Maternal pregnancy sample	Wk 17-20	EDTA blood, urine*	93 500	87,4%
Paternal sample	Wk 17-20	EDTA blood	67 800	81,5%
Maternal birth sample	0-3 days after birth	EDTA blood	83 500	78.0%
Child umbilical cord sample	Day of birth	EDTA blood, **RNA Tempus whole blood	89 600	82,5%
Child milk teeth sample	6-7 y	Milk teeth	5 788	24,2%

*Urine taken from a sub-group of 66.830 mothers
**RNA taken from 45.538 children

Linkage to registries

Data from the standard notification form of the child's birth from the Medical Birth Registry of Norway (MBRN) is included in the MoBa database. The Norwegian Data Inspectorate has granted a concession for this. This is an important link, as it will prevent the project from contacting the parents of children who have died at, or soon after birth, as well as allowing the identification of multiple births.

Links to health registries, other than MBRN, must be approved by the MoBa SMG, the Regional Ethical Committee (REK) and the owner of the register concerned. Also linking of MoBa data and MBR from the mother's own birth record requires approval from REK and MoBa SMG. At present, MoBa data have been linked with the Norwegian Prescription Database and the Cancer Registry.
Once a link is approved for one study it may be referred to when applying for equivalent studies.

Organisation

NIPH Executive Group is the steering committee. This group consists of the Director General of the NIPH and the division Directors (divisions: administration, epidemiology, mental health, environmental medicine, infectious disease control, forensic toxicology and drug abuse). Twice a year, the financial situation, progress reports and any important strategic questions are presented to the steering committee. The committee appoints the Principal Investigator (PI) and the members of the scientific management group (SMG).

The PI has the following responsibilities: To initiate and supervise MoBa-operations in a way that attends to high quality, to prepare documents for decisions in the SMG and the steering committee, to prepare budgets and financial strategies and to stimulate research activities.

The SMG consists of representatives from the scientific divisions of the NIPH. Their main task is to approve or reject applications for access to MoBa data and biological material in accordance with the conditions for access to data (Appendix 3). If necessary, external assistance will be sought before decisions are made. The approved projects are regarded as MoBa sub-studies. Furthermore, the SMG has an obligation to make MoBa data easily accessible for approved Norwegian and international research projects, to resolve potential conflicts of interest between sub-studies by specifying objectives and by encouraging co-operation, to stimulate research applications to Norwegian and international funding institutions and to make a research strategy for MoBa and guidelines for access to data and biological material. They should also encourage the creation of new projects within and across the divisions of the NIPH and to evaluate publications based on MoBa, in particular to pay attention to whether the objectives employed are congruent with those set forth in contracts, and to ensure that MoBa is appropriately presented.

MoBa is being run as an institute integrated study within the NIPH. The Division of Epidemiology is responsible for the management of MoBa. The administrative manager and two adviser positions are devoted to the day-to-day operation. This team holds the responsibilities for the handling of research applications for access to data and biological material. They are responsible for following up ongoing projects in MoBa as well as for maintenance and revision of the administrative quality documents. MoBa has employed staff in Bergen to manage the tracking system, data collection and the database. The Biobank containing the biological samples from MoBa is run by the NIPH and is located in Oslo. MoBa also collaborates with internal staff at NIPH for assignments concerning communication and economy. Names and contact information for present SMG members and staff are provided in Appendix 5.

Regulatory approvals

The Norwegian Data Inspectorate is the legal authority regulating MoBa. MoBa obtained an extended license from the Norwegian Data Inspectorate on 28th January 2010. The license is only valid for a limited time due to pending changes in the Norwegian legislation regarding the regulation of MoBa and other Norwegian health registries. MoBa obtained a positive ethical consideration from the Regional Ethical Committee for Medical Research (REK) in 1996 and 1998. MoBa is responsible for conducting the project in accordance with national legislation and international ethical standards. This implies that MoBa has ongoing contact

with the Norwegian Data Inspectorate and REK.

Access to data and/or biological specimens

All use of data should be in accordance with Norwegian and international legislation and guidelines for epidemiologic research. All research should be based on respect for the well-being and integrity of the participants. The Director General at the NIPH is responsible for the MoBa database.

Researchers can apply for access to data. Any access to data will be considered as a sub-study of MoBa. For each sub-study, a contract will be written between the NIPH and the PI of the research project and his/her research institute. The agreement regulates the right to study one or more specific research questions during a defined limited period of time. All sub-studies that use MoBa data must have a defined scientific administrator or institution responsible for the necessary legal and ethical approvals, and a PI with scientific responsibility for the project.

In addition to access to data, the researchers may apply for use of the collected biological material. Projects that perform analyses on the biological material will have exclusive rights to the obtained results for a limited time period as regulated in the collaboration contract with NIPH. Results of the analyses, including the description of methods and its quality parameters, will subsequently be made available for other studies. Results from analysis of biological material will be stored in the MoBa database. Large amounts of results from genome wide association (GWAs) studies and DNA sequencing will be stored in appropriate facilities that provide secure storage and access to the data. All results will be harmonized so they can be linked with health data from the questionnaire database. Merged data of questionnaire and analytic results can be applied for by researchers and will be available according to contracts.

Information on access to MoBa data and how to apply for data are described in MoBa conditions for access to data and biological materials (Appendix 3).

All approved sub-studies in MoBa are registered in a project database at NIPH, and given a unique reference number. An updated list of all sub-studies with the names of principal investigators and titles of sub-studies will be posted on www.fhi.no/moba. A list of publications based on MoBa data will also be found there.

Sub-cohorts

There are several sub-cohorts based on MoBa data. The sub-cohorts focus on particular exposures and/or outcomes. Sub-cohorts are conducting separate data collections, covering new data and biological samples, in addition to MoBa data. Such sub-cohorts use the MoBa infrastructure, but are organised as a separate research project with a steering committee and a research protocol, and they have their own regulatory approvals. Access to data from the sub-cohorts is governed by the steering committee in each sub-cohort and the MoBa SMG.

Ethics and regulations

Informed consent
Participation in MoBa is voluntary and based on informed consent. The participants agree to donate biological material and information about themselves. The participant may at any time withdraw from the study. Data already included in data analyses will not automatically be deleted, unless the withdrawal specifies this.

Children are included after consent from the mother. Children will be informed personally about the study when they are 15 years. Once the child reaches18 years old, MoBa will need informed consent from the child for further storage of the data.

New sub-studies, which require active participation (completion of new questionnaires, clinical investigations, evaluation of exposure or new biological samples) beyond that explicitly stated in the signed consent form, will require a new consent. The consent should also include access to transfer new data into the main database. Sub-studies that require collection of new data will need approval from REK. As a main guideline, invitations to participate in sub-studies will be sent by post to avoid undue influence of the researcher on the participant. Only the MoBa data management unit will be able to identify and contact the participant.

Participants can be recruited to sub-studies on the basis of disease information (e.g. pelvic pain or incontinence) or pregnancy outcomes about which they are already informed (e.g. congenital abnormalities) or based on geographical location, child's date of birth etc. As a guiding principle, recruitment cannot occur based on lifestyle habits; for example, smoking. If participants are to be recruited on the basis of findings from blood- and urine analyses, they must previously have given written consent stating that they are aware that they will be informed of the results of the blood- and urine analyses.

Protection of personal information
Inclusion in the cohort is through recruitment and informed consent of the pregnant woman. All information about the father and child will be linked to the woman, who is the index person in the project. Women who participate in the study are registered in a database containing name, personal identification number, a code number which corresponds to other files, information relating to when questionnaires or blood- and urine samples are sent and received, and whether reminders have been sent. No other information is stored in the personal identifiable database (the tracking system – see Appendix 1).

All personal identifiers will be removed in the main database (Appendix 1). Identification of participants will only be possible by a few dedicated data managers for data collection purposes. No personal identification data will be sent to researchers.

Advantages of MoBa
The purpose of the project is to investigate the causes of disease. Knowledge about the causes of disease can lead to better interventions, and further laboratory research which can reveal both the mechanisms that underlie disease processes, and lead to new treatment forms. It is also important to disprove false theories regarding the cause of disease and investigate which factors promote good health and absence of disease. Increased knowledge about medical and sociological science is essential for the understanding of illness in the community.

Potential Disadvantages
No interventions will be undertaken in connection with the project, in the sense that conditions resulting in an exposure will not be wittingly modified in order to prevent disease. Participants will not routinely receive the results of blood tests, or other information about themselves, that they are not already aware of. However, the participant has the right to know what information is stored about him or her in the database. The individual participant will as a general rule not have any direct health benefit from the project.

MoBa is obliged to inform the participants of the use of data, and the outcome the research. This information will be available through newsletters and on MoBa's internet page. In addition, news from MoBa will be presented in newspapers and other media.

Some participants may find certain questions intrusive, others may find that the scope of the questionnaire is wider and that they are to be completed more frequently than they had expected. The participants are asked to answer as fully as possible, but they will not be contacted if any answers are incomplete. If participants do not answer the questionnaire for one age group, data already collected will remain in the database and a new questionnaire will be sent when the child reaches the age for the next questionnaire.

International collaboration

In 2001, the NIPH entered into a contract with The National Institute of Environmental Health Sciences (NIEHS). The purpose of the contract was to support the running of MoBa, and specifically to collect biological material suitable for analysing associations to environmental hazards. In 2007 a new contract was signed. This contract will run for ten years, from May 2007 to April 2017, again to support the collection, processing, storage and access to biological specimens. In addition, the contract includes options to support research sub-studies, validation studies and additional data collections. A Memorandum of Understanding between NIEHS and NIPH formulated terms of scientific collaboration within the framework of MoBa. The particular interest of NIEHS is in environmental exposures that may affect foetal, childhood or adult health, and in genetic susceptibility to such effects. In order to strengthen MoBa in this area, NIEHS proposed to fund the collection of one extra maternal blood sample and one urine sample during pregnancy, to be stored in Norway for eventual assessment of environmental exposures. While these samples would be prioritised for use in NIEHS-initiated studies, they would be accessible to Norwegian researchers with NIEHS approval and in collaboration with NIEHS researchers. Conversely, any use of these specimens by NIEHS would be in collaboration with Norwegian researchers. In several research areas there are established projects including international and national collaborators based on this contract.

In addition to this collaboration, MoBa has agreements and collaborations with several international research groups, often through grants from the National Institutes of Health in the USA or through the Framework Programs of the European Union.

Funding and costs for retrieval of data and biological material

The MoBa project has no fixed public funding, but has been supported by various collaboration projects, project-based governmental support and international grants. In the future, management of MoBa will also depend on external funding. All researchers using MoBa data are encouraged to apply for Norwegian and international funding.

Due to MoBa's financial situation there is an administration fee for access to questionnaire data and biological samples. The latest MoBa price list can be found on the web page www.fhi.no/moba

Publications policy

MoBa's publication policy for researchers is found in the MoBa conditions for access to data and biological material (Appendix 3).

All manuscripts and abstracts should be revised by the MoBa SMG before publication to assure that the description of MoBa is correct and that the analyses are in accordance with the scientific aims of the study agreement. The NIPH will not intervene in the scientific content of the publication.

MoBa is obliged to inform the participants of how MoBa data are used. A brief description of ongoing sub-studies will be posted on the website. MoBa will also request a short summary of sub-study results, written for the general public, which can be posted on the webpage.

Appendixes:

Appendix 1: Tracking system and database
Appendix 2: The Biobank
Appendix 3: MoBa Conditions for access to data and biological materials
Appendix 4: Consent forms
Appendix 5: Contact information

Appendix 1: Tracking systems and database

Introduction
The Norwegian Mother and Child Cohort Study has two main IT-systems, *MoBaStudy* and *MorBarnData,* to administer participants, their questionnaires and biological samples. In addition to the two main systems, other systems are Readsoft Eyes and Hands™ for scanning paper-based questionnaires, several web applications for online questionnaires and web-based applications for coding labor and medication.

MoBaStudy

MoBaStudy is a logistic system for keeping track of all participants, their status, questionnaires sent and returned, assessments like ultrasound appointments, participation in sub-studies and a laboratory information management system (LIMS) for handling biological samples and sample pulls.

The system generates questionnaire dispatchments with barcodes and cover letters based on user-defined dispatchment rules. All user interface labels, menus and messages are defined in the database and can be changed to specific needs. User rights to all interface components are also defined in the database. Functionality also includes dual language support, option for loading new participants from text files, standard- and user-defined reports, and communication with laboratory robots and other equipment. All data changes are logged in an audit table so a complete audit history is available for all data fields. *MoBaStudy* also contains a portable PDA version *PDALab* used for off-site sample pulls.

The main key for the system is *StudyUnit*; each pregnancy is assigned a unique *StudyUnit_ID* and each person has a role in a *StudyUnit*; mother, father or child.

The data in *MoBaStudy* consists of personal identifiable information; names, addresses, social security numbers, phone numbers etc., and for that reason do not include any sensitive health information.

MorBarnData

All sensitive health information; questionnaire data, medical records and results from sample analyses are kept in *MorBarnData*. *MorBarnData* contains no personal identifiable information and is physically separate from *MoBaStudy*. The two systems use different database technology and are located on completely different servers (Oracle 11G on Unix and MSSQLServer 2005 on Windows 2008 Server). Both systems have their own separate built in user authentication, and database access is only enabled through the applications.

The main key in *MorbarnData* is *Stud_ID* and is different from the main key in *MoBaStudy*; *StudyUnit_ID*. The linkages between these keys are stored in the *MorBarnData* database and are nowhere available through the user interface. This secures that the health information in *MorBarnData* is anonymous.

MorBarnData automatically creates storage space for scanned questionnaires based on Eyes & Hands description files or regular text files. The system also keeps track of different

version of questionnaires by linkage between equivalent fields in the different versions. *MorBarnData* has meta data in both English and Norwegian, functionality for quality control and an image viewer. All data changes are tracked and the system has a data extraction (shopping list) functionality that creates *SAS* and *SPSS* data files with metadata (variables and values labels) or regular text files.

All data from scanning paper based questionnaires are transferred to text files and loaded into *MorBarnData* and linked to the correct *Stud_ID* based on the questionnaire barcode. While loading, the data is automatically tested for validity against user-defined quality control rules. Quality control tasks are created for each field containing errors. These error tasks must be solved by verifying values against scanned images before the questionnaire data can be used.

Both systems are completely dynamic and can be used for any similar study using biological samples and questionnaires. Currently the systems are used by 3 independent studies. One important feature is the ability to track a person's history, not just the history of the pregnancy (Study units's). A person can be a child in one pregnancy (study unit), and later be a parent in a future pregnancy (study unit).

Appendix 2: Biobank description

Overview

Established in 1999, the Biobank at the NIPH has grown to become a state-of-the-art unit for long-term storage and processing of valuable biological samples used in national and international research. The Biobank is responsible for all biological specimens collected through MoBa.
The Biobank has three main responsibilities in the MoBa study:

- Sample handling, processing and long-term storage of the collected biological specimens for current and future use.
- Quality assurance and quality control of the banked biological samples by implementation of evaluative procedures to determine sample quality with respect to specific uses.
- Retrieval of requested biological material for national and international researchers for specific analyses.

The collection of samples is described in details in MoBa study protocol I (enrolment), last revised June 2008. In brief, EDTA whole blood samples were collected from both parents during pregnancy, from the child's umbilical cord at birth, and from the mother post-partum. DNA has been extracted and plasma separated. From the child, umbilical cord blood was collected in TEMPUS blood tubes for RNA extraction and gene expression studies. The RNA collection was initiated in 2005, and RNA samples are available for approximately 45.500 children included in the cohort. A urine sample was also collected from the mother during pregnancy (prenatal). DNA and some of the whole blood are stored at -20 ºC, while RNA, whole blood, plasma and urine are stored at -80 ºC. The blood samples available in MoBa are suitable for genetic analyses, transcript profiling, biomarker analyses and toxicology analyses. In addition, milk teeth from children at 7 years of age are collected, and stored at the University of Bergen, institute of odontology.

Methods for sample collections have changed over the course of MoBa due to expanding research interests and technology:
June 1999
Blood from mothers at 17^{th}-20^{th} week of gestation (2 x 7 ml EDTA whole blood)
Cord blood from children at birth (2 x 7ml EDTA blood)
Autumn 2000
Blood from fathers at 17^{th} -20^{th} week of gestation (2 x 7 ml EDTA whole blood) 20^{th}
January 2002
Environmental samples of whole blood and urine from mothers at 17^{th} -20^{th} week of gestation:
7 ml heparin blood + 3 ml EDTA blood + 10 ml urine in clean tube
May 2003
Change in environmental samples to 7 ml EDTA + 3 ml EDTA + 8 ml urine in tube with chlorhexidine
May 2005
Change in cord blood samples to 10 ml EDTA tube + 3 ml TEMPUS RNA collection tube
Feb 2008
A milk tooth is collected from all the children at 7 years of age.

The MoBa study is unique among established prospective birth cohorts. The collection of data and biological specimens in MoBa began during pregnancy, and not from birth, as for most other child cohort studies, which gives excellent opportunities to study prenatal exposures. MoBa is also the only cohort study that is collecting blood samples for RNA extraction and gene expression studies. Whole blood samples in TEMPUS blood RNA tubes are available from children born during or after September 2005. In addition, whole blood samples, and thus extracted DNA, from the fathers are also available, which gives the opportunity for genetic studies including the mother, father and child (triad design). Linkage to the central health registries in Norway is possible because every citizen in Norway is allocated a unique person identification number at birth. Data from the Medical Birth Registry in Norway (MBRN) is included in the MoBa study.

Sample handling and storage of biological material in MoBa
The sample handling and processing of biological material from the consenting participants in the MoBa study are described in detail in the MoBa Study Protocol I (enrolment), last revised June 2008, and in Rønningen et al. (2006). In addition, the Biobank operates with standard operation protocols for all specimen handling. In brief, collection of MoBa samples was performed at hospitals where subjects were recruited, and shipped to the Biobank overnight in packaging provided by NIPH. Most samples were received the day after collection. However, blood samples collected during weekends were stored for up to two days at + 4°C prior to transportation to the Biobank. The transport of blood samples from the hospitals to the repository was performed by regular mail at ambient temperature due to seasonal changes in Norway. The specimens may therefore have been subject to elevated temperatures for variable intervals before arrival at the Biobank.

All biological specimens collected in the MoBa study were registered into a secure data-management system on arrival. Barcode labelling is used on all samples and storage equipment to ensure the security and traceability. The specimen processing and storage took place upon arrival at the Biobank. DNA was isolated from whole blood samples within a maximum of 5 days. Thus, all aliquoted samples were stored within specified time limits to ensure quality.

Aliquoted samples are assigned to freezers with optimal storage temperature for each sample type. Back-up freezers are available in case of freezer failure. Continuous temperature monitoring is in operation, and duplicates of material from the same individual are stored in separate freezers for security purposes.

New collections of additional biological material from the participants when the children grow up will be considered if scientifically relevant and funding is available.

Status for collection of biological samples

The repository database registers all biological samples received by MoBa. As of October 2010 a total of 67.800 fathers' samples sets were registered. In addition 93.5000 maternal sample sets taken at around week 17 of pregnancy, and 83.500 maternal sample sets taken after delivery were registered. 89.600children's sample sets were registered. Of the 90.725 women are participating in the MoBa cohort, 75.470 women participate with one pregnancy and 15.255 women with two or more pregnancies. 1871 twins and 21 triplets are included,

which gives opportunities for sibling studies and genetic studies of twins/triplets. (Table 1 in revised protocol II October 2010)

The biological specimens available in MoBa

The biobank constitutes different sample types which are stored in different volumes and concentrations, as well as in different formats (Table 1 - Appendix 2).

Table 1- Appendix 2.
The different human biological specimens collected in the MoBa study

Sample	Aliquoting*	Storage format	Temp
Whole blood (K1, K2, F, N, A)	2 x 930µl	Plates with 96 wells	-80°C
Plasma (K1, K2, F, N, A)	6 x 300µl	Plates with 96 wells/ single matrix tubes**	-80°C
DNA (K1, K2, F, N, A)	5 x 930µl *** Approximate concentration 100ng/µl	Plates with 96 wells	-20°C
RNA Tempus Whole blood (N, A)	1 x 3ml	In the collection tubes	-80°C
Plasma (K1 environmental sample)	3 x 930µl****	Single matrix tubes	-80°C
Whole blood (K1 environmental sample)	1 x 3ml	In the collection tubes	-20°C
Urine (K1 environmental sample)	8 x 930µl*****	Single matrix tubes	-80°C

* This is the max volume aliquoted. Where less material was available the volume has been registered in the data-management system.
** Single tubes were introduced February 2008.
*** The volume of DNA will vary based on the DNA yield. In cases where there has been a lot of DNA up to 10 wells may have been aliquoted.
**** May 2003 the sample material was changed from plasma heparin to plasma EDTA. Before September 2005 the aliquoting was 3 x 750µl.
***** May 2003 the collection tube was changed from a 10ml tube without additives to a 8 ml urine in tube with chlorhexidine. Before July 2008 the aliquoting was 6 x930µl.

K1: Sample from the mother at ultrasound, week 17th – 20th of pregnancy
K2: Sample from the mother post-delivery
F: Sample from the father
N: Cord blood
A: Sample from 4 year old children included in the Autism Birth Cohort Study (ABC),

Quality Assurance (QA) in the Biobank

The Biobank has well-established routines and back-up facilities to ensure the safe storage and processing of biological samples and is aiming for ISO 9001:2008 certifications in 2011. All equipment is regularly maintained for optimal performance.
The following measures have been implemented to reduce the risk of damage to the stored material:
- Sample processing and handling are expedited by using computer supervised/robotic systems
- All laboratory procedures are performed by standard operational procedures (SOPs)
- Freezers have back-up generators and alarm systems for temperature monitoring
- Samples from each individual are split and stored in separate freezer units.

QA/Quality Control (QC) of the banked specimens

Safeguarding of the biological material collected in the MoBa study with high standards of quality is of the utmost importance. Storage of MoBa biological specimens banked for use in current and as yet undetermined hypotheses raises issues concerning the samples' integrity. The repository has a quality control program, as well as ongoing QA/QC projects to document the quality of the biological specimens.

DNA was extracted from whole blood samples from both adults (parents) and whole blood obtained from the umbilical cord using commercially available products, and was normalized to 100 ng/µl, ±20 ng/µl using semi-automated processes. The Biobank has established a QC program for DNA samples where samples are tested for DNA concentration, purity, PCR success rate and fragmentation. The DNA is stored in aliquots on 96 deep well plates at -20°C. However, the Biobank is planning to make some of the DNA from each individual available at a concentration of 25 ng/µl.

Analysis of a selection of biomarkers after freeze-thaw cycles have been conducted at the MoBa Biobank. Results indicate that most of the tested biomarkers remain stable in plasma after 30 freeze-thaw cycles (Paltiel et al., 2008). Information about the stability of analytes may influence choices of samples for specific analyses. To avoid unnecessary freeze-thaw cycles, the regular MoBa plasma samples will be moved from 96 wells microtitre plates onto single tubes on Matrix plates, equal to the environmental plasma samples. Planning of this process is in progress. The process will involve thawing the samples before transfer to single tubes prior to re-freezing.

A program for monitoring a selection of biomarkers in urine and plasma during long-time storage has been established. The analyses are done once a year.

Umbilical cord blood from the child has been collected in TEMPUS blood RNA tubes (Applied Biosystems) for later RNA extraction and gene expression studies. For quality control the Biobank compares the quality and stability between long-term stored umbilical cord blood collected on RNA TEMPUS tubes and long-term stored extracted RNA. This study is ongoing and the results will be published in scientific journals. The RNA specimens will be available to research projects in the near future.

Retrieval of requested biological specimens for researchers

Interest in the use of the biological material for research purposes to test specific hypothesis is increasing. Unlike data from questionnaires which can be reused, biological material is a limited resource. Guidelines for access to data and human biological material are available in the MoBa conditions appendix 3.

Retrieval of biological material for researchers that apply for access is ongoing, and is performed both manually and with partially automated equipment for all samples stored in 96 well format. Remaining materials are returned to long-term storage. The entire process is recorded in the tracking database, creating an up-to date inventory.

The Biobank was recently awarded governmental funding for an automated -20°C storage freezer system for retrieval of requested samples. The automated storage system will be installed during spring 2011. This will increase the speed and capacity of retrieval of requested samples, and will assist in quality assurance.

To avoid emptying the Biobank of biological specimen from the participants due to future scientific needs, a minimum amount of plasma, DNA, and whole blood will be retained from each participant, both adults and children. In addition, some biological samples (urine and whole blood samples for environmental analyses, RNA) were collected through international co-operation, and therefore special access rules apply. This is described in the conditions for access to human biological material collected in the MoBa study. A price strategy for access to biological material is also available at our website (www.fhi.no/moba).

Website for the Biobank

A more detailed description of Biobank conducted by The Norwegian Institute of Public Health is available at our website. (www.fhi.no/)

References

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: a resource for the next 100 years.* Eur J Epidemiol. **2006**;21(8):619-25. Epub 2006 Sep 20.

Paltiel L, Rønningen KS, Meltzer HM, Barker SA, Hoppin JA. *Evaluation of freeze-thaw cycles on stored plasma in the Biobank of The Norwegian Mother and Child Cohort Study*. Cell Preservation Technology **2008**; 6:223-230.

Appendix 3 MoBa Conditions for access to data and biological materials

20th Dec 2010

THE NORWEGIAN MOTHER AND CHILD COHORT
TERMS AND CONDITIONS FOR ACCESS TO DATA AND BIOLOGICAL MATERIALS

Table of contents

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 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 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 Collaboration 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.
Collaboration Agreement	Agreement regulating the execution of a Sub-study; signed by the NIPH and the Sub-study institution.
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 Collaboration 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 (enrolment), last revised June 2008, and the end of inclusion protocol II of November 2010 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 is	*Charges for MoBa data and biological materials. The price list* 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. 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 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. 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 MoBa SMG prior to submission of applications to the REK and other regulatory bodies.

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. The MoBa 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. MoBa Collaboration 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 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 MoBa data and BM (*Sections 8, 9, 13, 15*).

MoBa 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, but other time intervals may be chosen, depending on the nature of the Sub-study. If an extension of the agreement is required, an application must be sent to the MoBa SMG prior to the expiry date of the original Collaboration Agreement.

The MoBa 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 MoBa SMG prior to the submission of any publications. If suggested changes are approved by the MoBa 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 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 a Collaboration Agreement is signed, the NIPH reserves the right to adjudicate between different proposals. A 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 listed in the Collaboration Agreement will be submitted from the MoBa Data Center 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 anonymized. In some cases, de-identified are required to link data from different Sub-studies, to update 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 file will contain data from the last updated source files, unless otherwise specified in the Collaboration Agreement. 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. 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.

f. 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, 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 Collaboration 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. 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. 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 Collaboration Agreement.

11. Regulatory approvals and linkages to other registries

MoBa is regulated by the Norwegian Data Inspectorate. The current license was obtained in January 2010. 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.

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 Collaboration Agreement 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. The MoBa SMG has a restrict policy when it comes to publishing the direct effects of confounding variables, in order to avoid infringement on other sub-studies. Such information may be submitted to referees/editors if required.

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) conducted by the Norwegian Institute of Public Health.

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, and 38.5% of invited women consented to participate. The cohort now includes 108,000 children, 90,700 mothers and 71,500 fathers. Blood samples were obtained from both parents during pregnancy and from mothers and children (umbilical cord) at birth. Follow-up is

conducted by questionnaires at regular intervals and linkage to national health registries. Several Sub-studies are conducting additional collections of data and biological materials.

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). Informed consent was obtained from each MoBa 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 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-85433), NIH/NINDS (grant no.1 UO1 NS 047537-01), and the Norwegian Research Council/FUGE (grant no. 151918/S10). 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.*

Posters and abstracts do not require approval from the MoBa SMG, but a copy must still 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 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 MoBa SMG confirming that this procedure has been conducted. If the Sub-study 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 for the general public at most one page must be submitted to dataaccess@fhi.no. This report will be published on the MoBa 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 MoBa 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 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

Collaboration 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 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.

Appendix 4: Consent forms

Informed consent form - mother

I have read the letter inviting participation and the information brochure about the Norwegian Mother and Child Cohort study and understand that the information I give will be treated strictly confidentially. I am aware that the project has been approved by the Regional Ethics Committee for medical research and by the Norwegian Data Inspectorate.
Participation in the Norwegian Mother and Child Cohort Study will entail the following:

- that I complete questionnaires, during and after pregnancy, about my own and my child's health and living conditions
- that I give a blood sample and a urine sample, during pregnancy and one after the birth, and that a sample is also taken from the umbilical cord at birth
- that the blood samples from myself and my child will be stored and used for future research to study causes of diseases, including heredity. Laboratories in Norway and other countries will carry out this research following approval by the Regional Ethics Committee for Medical Research and the Norwegian Data Inspectorate that the blood samples can be used for this purpose.
- that the results from ultrasound examinations carried out during the pregnancy will be made available to the project
- that the blood sample which is taken from my child to test for PKU (phenylketonuria) may be made available to the project
- that no results (either concerning my own or my child's health) will be sent by the project to me
- that information about myself and the child can be obtained from other sources, for example the Medical Birth Registry of Norway and hospital records, following approval by the Norwegian Data Inspectorate
- that I may be asked to participate in further projects where I will be required to give additional information (or biological samples). Participation will be voluntary, and all such additional projects will satisfy conditions laid down by the Norwegian Data Inspectorate and the Regional Ethics Committee for medical research
- that information and blood samples will be stored indefinitely. This is a long-term study that will also investigate the reasons why diseases occur in adulthood. My child will be informed about the project when he/she is 15 years old, and consent requested from the child that he/she remains in the project when they are 18 years old
- that no information or biological samples will be made available to researchers before name and personal identification number have been removed
- that participation is voluntary and that I can withdraw from the study at any time by writing to the Norwegian Mother and Child Cohort Study.

I have read the information above and agree to participate in the Norwegian Mother and Child Cohort Study.
Name: _____
Personal identification number *(11digits)*:_____
Date:_____ Signature:_____

My address on the invitation letter is wrong, the correct address is:

_____

Informed consent form - father

I have read the introduction brochure concerning the Norwegian Mother and Child Cohort Study and understand that the information I provide will be handled strictly confidentially. I understand that the study has been considered by the Regional Committee for Ethics in Medical Research and approved by the Data Inspectorate of Norway.

Participation in the Norwegian Mother and Child Cohort Study requires the following:

- that I complete the questionnaire concerning my own health, life style and working environment
- that I provide a blood sample at the time of the ultrasound examination
- that my blood sample will be stored in a "biobank" at the Norwegian Institute of Public Health. The sample will have no personal identifiers and will be stored with a code number. The blood sample will be used solely for research purposes addressing causes of illness, including the interaction between genetic disorders and environmental factors. This will be conducted in laboratories in Norway and other countries after the specific use of the blood sample has been considered by the Regional Committee for Ethics in Medical Research and approved by the Norwegian Data Inspectorate
- that I will not receive any results concerning my health or from the analysis of my blood sample
- that information about me may be obtained from other sources such as the Medical Birth Registry of Norway and hospital records following approval from the Norwegian Data Inspectorate
- that I may be asked to participate in studies that require the collection of additional information (and samples). Such sub-projects will be considered separately by the Norwegian Data Inspectorate and the Regional Committee for Ethics in Medical Research. Participation is voluntary and is not necessary for continued participation in the main study.
- that the information and blood sample will be stored indefinitely
- that no information or samples are made available to researchers before my name and personal identification number are removed
- that I may withdraw from further participation in the study at any time by writing to or calling the Norwegian Mother and Child Cohort Study. In addition, I may request that information and blood samples collected be deleted/destroyed without providing a reason.

I have read the information and give my informed consent to participate in the Norwegian Mother and Child Cohort Study. (Please write clearly in CAPITAL LETTERS.)

Name:
Personal identification number (11 digits):
Address: Post code:
Partner's name:
Partner's personal identification number (11 digits):
Date: Father's signature:

Please return with the questionnaire.
Please keep this copy for your records.

Appendix 5: Contact information

MoBa Scientific Management Group

Dominique Caugant	Department of Infectious Diseases Control	Dominique.Caugant@fhi.no
Helle Margrethe Meltzer	Department of Environmental Medicine	Helle.Margrethe.Meltzer@fhi.no
Kristian Tambs	Department of Mental Health	Kristian.Tambs@fhi.no
Per Trygve Normann	Department of Forensics Toxicology and Drug Abuse	Per.Trygve.Normann@fhi.no
Marte Handal	Department of Epidemiology	Marte.Handal@fhi.no
Rolv Skjærven	Medical Birth Registry of Norway	Rolv.Skjarven@smis.uib.no

Deputies for the leader team

Ingeborg S. Aaberge	Department of Infectious Diseases Control	Ingeborg.Aaberge@fhi.no
Margaretha Haugen	Department of Environmental Medicine	Margaretha.Haugen@fhi.no
Heidi Aase	Department of Mental Health	Heidi.Aase@fhi.no
Silja Skogstad Tuv	Department of Forensics Toxicology and Drug Abuse	SiljaSkogstad.Tuv@fhi.no
Eirin Bakke		Eirin.Bakke@fhi.no
Wenche Nystad	Department of Epidemiology	Wenche.Nystad@fhi.no
Anne Kjersti Daltveit	Medical Birth Registry of Norway	Anne.Daltveit@mfr.uib.no

Project leader

Per Magnus	Per.Magnus@fhi.no

Administrative leader

Charlotte Birke	Charlotte.Birke@fhi.no

Advisors

Anita Haugan	Anita.Haugan@fhi.no
Kristine Vejrup	Kristine.Vejrup@fhi.no

MoBa data centre

Patricia Schreuder	Patricia.Schreuder@fhi.no
Elin H.R. Alsaker	ElinHildeRoti.Alsaker@fhi.no
Nina Hagsæther	niha@fhi.no
Ole Martin Kvinge	Ole-Martin.Kvinge@fhi.no
Arild Sunde	Arild.Sunde@fhi.no

Biobank

Kari Harbak	Kari.Harbak@fhi.no
Liv Paltiel	Liv.Paltiel@fhi.no

Questionnaires and patient information

Jorid Eide	Jorid.Eide@fhi.no
Kari Kveim Lie	KariKveim.Lie@fhi.no

Communication

Torunn Moe	Torunn.Moe@fhi.no