Meeting report on

CONSULTATION ON STANDARDIZATION OF RESEARCH METHODS RELATED TO THE CONTROL OF HEREDITARY DISORDERS

Alexandria, Egypt, 12-15 November 1995
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1. INTRODUCTION

A regional consultation on standardization of Research Methods Related to the Control of Hereditary Disorders was organized by the WHO Regional Office for the Eastern Mediterranean (EMRO) in Alexandria from 12 to 15 November 1995. A list of participants is given in Annex 1.

The WHO consultation on community genetics services in the Eastern Mediterranean Region (EMR), which was held in April 1994, concluded that available evidence showed a particular need for genetics services throughout the Region. The additional needs arise because of several risk factors that include the high frequency of advanced parental age, haemoglobin disorders, and customary consanguineous marriage. In many countries medical services have reached a standard such that many patients who would formerly have died are now surviving, and the number of children with chronic disorders (and so the costs for their treatment) is rising progressively, with important resource implications. Epidemiological studies of the prevalence of congenital and genetic disorders are now needed in each country in order to estimate present and future service needs.

Some countries have already collected much relevant information, and some already plan registries of congenital anomalies and of specific genetic diseases. These, and other relevant research studies that have been initiated in some countries, should be promoted and extended. However, there is a general lack of accurate and standardized epidemiological data for the EMR, that can be used to evaluate the health burden of congenital and genetic disorders, and to plan appropriate services. The following recommendations were therefore made for research on the epidemiology of these disorders in the Region.

1. Basic demographic data relevant to the frequency of genetic disorders should be collected by appropriate centres in each country. Such data should, for example, include parental age distributions and prevalence and types of consanguineous marriages.

2. Studies are needed of the relation between these demographic factors and morbidity and mortality at birth, in childhood, and in adult life in the countries of the EMR. Research protocols should be standardized for use throughout the Region, to generate comparable data and allow collaborative studies.

3. Studies are urgently needed on the prevalence of maternal risk factors such as teratogenic maternal infections, diabetes, and iron, iodine and folate deficiencies.

4. Studies are needed on the frequency and sequelae of genetic causes of neonatal jaundice; for example, blood group incompatibility, glucose-6-phosphate dehydrogenase (G6PD) deficiency and rare single gene defects.

5. Newborn screening is a useful research tool for establishing the frequency of G6PD deficiency, sickling disorders and some metabolic disorders, all of which are particularly important in the Region. A collaborative research project on newborn screening may be considered.
6. Studies are needed of the frequency of congenital abnormalities that are not readily diagnosable at birth, such as mental handicap, impairment of hearing and sight, congenital heart disease, etc.

7. Registers of patients with common congenital and genetic disorders that can be readily and accurately diagnosed, such as Down syndrome, haemoglobin disorders, some inborn errors of metabolism, and other congenital anomalies should be established in each country. The purposes of the national or local registers are (a) to establish the epidemiology of the commonest congenital anomalies in the EMR, (b) to provide a basis for assessing present and future service needs, (c) to compare data with that from other areas and Regions, and (d) to establish methodology for registers of other genetically-determined disorders such as familial cancers.

8. To facilitate diagnosis, a standardized protocol for non-invasive post-mortem examination of late miscarriages, still births and infant deaths should be developed, for use throughout the Region.

Data should be collected using standardized protocols in order to obtain comparable data, and should take account, whenever possible, of local population characteristics such as geographic and ethnic factors, and should permit micro-mapping of disorders.

2. OBJECTIVES

The objective of this consultation was to initiate the development of standardized methods for data collection and analysis on these topics outlined in the introduction in the countries of the Region.

Much of the data required for mothers and babies can appropriately be collected around the time of delivery, by health professionals involved in the care of the mother and her baby. Data sets 1–5 outlined in the introduction come naturally together as components of a single "Mother and Baby" study, and the development of a draft protocol for such a study was the main task of this consultation. Clearly additional protocols (for data sets 6 onwards) are required to ensure comprehensive data collection on epidemiological aspects of congenital and genetic disorders. Several relevant protocols have been developed, or are in process of development by WHO/EMRO (e.g. the WHO/PBL eye examination record for children with blindness and low vision).

The protocol for the mother and baby study is therefore identified as Protocol No 1 in a possible series of standardized protocols for gathering information on the health burden of congenital and genetic disorders in the Region, including common diseases with a genetic predisposition.

A draft protocol and questionnaires for the EMRO Mother and Baby study developed during the consultation are presented below together with a draft manual of operations, draft protocols for the optional components of the mother and baby study and additional studies for which protocols may be developed. The further work required on the manual of operations and teaching package, and development of computer software should be carried out at a later stage.
DRAFT PROTOCOL
1. OBJECTIVES AND GENERAL STRUCTURE OF THE STUDY

This is a multicentre prospective epidemiological study of the birth prevalence of congenital and genetic disorders in the countries of the EMR.

The study is descriptive and its purpose is to provide local information that will assist governments in planning, implementation and monitoring of a public health programme of appropriate genetics services for babies and their families.

The study will involve local health workers being trained to collect data and examine newborns, and will raise clinical awareness of congenital anomalies and their importance as a cause of mortality and morbidity.

Objectives

There are six basic objectives in the study. Only objective 1 is a core objective to be carried out by all participants. The other objectives can be met as options at varying levels according to the resources available to each study team.

Core objective (Objective 1). To gather basic demographic data on parents, including data on parental consanguinity

Objective 2 (optional). To establish the prevalence (on a community, geographical base wherever possible) of structural congenital anomalies detectable at birth by clinical examination of newborns, including stillbirths.

Objective 3 (optional). To establish the prevalence of risk factors for congenital anomalies in mothers through blood testing (for example, haemoglobin disorders, rubella and other maternal infections, folate and iodine levels, and G6PD deficiency).

Objective 4 (optional). To establish the birth prevalence (on a community, geographical base wherever possible) of haemoglobin disorders, G6PD deficiency and some metabolic disorders, by analysis of Guthrie blood spot samples in newborns, including stillbirths.

Objective 5 (optional). To establish the frequency of antenatally diagnosed congenital anomalies in the study population.

Objective 6 (optional). To link the later outcome in the babies with parental demographic data, and to establish the prevalence of genetic disorders and congenital anomalies which can only be diagnosed after the neonatal period.

Standardized methods will allow pooling of "core" and optional data across the Region.

2. STUDY DESIGN

The core study of the target population can be set up either (a) using anonymous data only, for purely epidemiological purposes, or (b) using named data, in order to allow the possibility of follow-up of target babies. Research teams need to look carefully at the advantages and disadvantages of each approach.
An anonymous study is the simplest to execute. Clearly, mothers and babies with abnormalities detected at the time of data collection must be referred for appropriate clinical management when possible. However, in an anonymous study it is not possible to arrange for follow-up of babies when abnormal findings emerge later, e.g. through tests carried out on the mother's blood, or on Guthrie cards.

Alternatively, when the initial investment has been made to carry out the initial epidemiological study, it may prove desirable and feasible in some areas to develop it into a prospective follow-up study of the cohort of registered babies, in order to identify congenital and genetic disorders that cannot be readily diagnosed at birth (such as many congenital malformations, thalassaemia, haemophilia, mental retardation, inborn errors of metabolism, blindness and deafness†). This can only be done by recording confidential details of the mother and baby, such as name and address.

With appropriate support, birth cohorts can be followed at regular intervals for a long period (e.g. the three UK birth cohorts (1947, 1958, 1970), still being followed at intervals, include a random sample of all babies born in one week of that year). Such studies give an increasingly valuable yield of health information with the passage of time.

It is essential for each study team to decide at an early stage whether they will conduct an anonymous core study, or a follow-up study, since the decision will affect all aspects of data collection. For example, if follow-up is contemplated, a parent's consent to all parts of the study, including later follow-up, should be obtained at the outset. If a team is undecided, a named study may be selected, since it allows room for a later decision to follow up the cohort.

Concerns about ethics and confidentiality

There are ethical issues and concerns about confidentiality for any study with named data, or studies where subjects can be identified through case numbers. In a named study, a parent will need an explanation of the study objectives before they can give informed consent. They also need to know if samples of either maternal or infant blood will be stored for future use. The consent of a parent may be refused for all or parts of the study and this will remove data on that mother and baby from results.

Measures to ensure confidentiality of study data are extremely important if named data are collected in order to facilitate follow up. These may include using stand alone computer systems and passwords, and avoiding accidental access to study data by setting up appropriate security systems.

Optional objectives

Each optional objective can be implemented at different levels, according to the resources available in each study centre. There are also choices within each level about the risk factors and diseases to be studied.

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† Separate epidemiological studies of such conditions may also be arranged with appropriate country specialists.
**Objective 2.** To establish the birth prevalence (on a community, geographical base wherever possible) of structural congenital anomalies detectable by clinical examination of new-borns, including stillbirths.

*Level 0* Omit this objective

*Level 1* Describe the birth population in terms of structurally normal and structurally abnormal stillborns and neonates. Record what abnormalities are found. (This may be the appropriate level in some studies based in primary health care in rural communities).

*Level 2* As level 1 plus immediate referral to a specialist in genetic diagnosis (usually a paediatrician) for investigation, diagnosis, counselling and any possible treatment of the abnormality. The specialist will keep a record of all children from the community identified through this initial screen, but will use an exclusion list when reporting cases for the study.

**Objective 3.** To establish the prevalence of risk factors for congenital anomalies in mothers through blood testing (for example for haemoglobin disorders, G6PD deficiency, rubella and other maternal infections, diabetes, folate and iodine levels)

*Level 0* Omit this objective

*Level 1* Store maternal sera for future testing

*Level 2* Test the maternal samples for carrier status for some genetic disorders and potentially teratogenic disorders, such as haemoglobin disorders, rubella, cytomegalovirus (CMV), toxoplasmosis and other maternal infections, diabetes, folate and iodine levels, G6PD deficiency and the hereditary anaemias.

**Objective 4.** To establish the birth prevalence (on a community, geographical base wherever possible) of haemoglobin disorders, G6PD deficiency and some metabolic disorders by analysis of Guthrie blood spot samples in newborns, including stillbirths.

*Level 0* Omit this objective

*Level 1* Establish a bank of Guthrie spots for later analysis

*Level 2* Collect Guthrie spots for analysis for disorders which may include haemoglobinopathies, G6PD deficiency and metabolic disorders

*Level 3* As for level 2, plus referral of possibly affected babies to a specialist for investigation, diagnosis, counselling and any possible treatment of the abnormality. This may include specific investigations to diagnose some metabolic disorders such as those included in Table 1.

**Objective 5.** To establish the frequency of antenatally diagnosed congenital anomalies in the study population.

*Level 0* Omit this objective

*Level 1* Report all structural abnormalities, including chromosomal markers, detected by ultrasound after the first trimester.

*Level 2* As level 1, plus reporting all chromosomal abnormalities, haemoglobin disorders and metabolic disorders detected by chronic villus sampling (CVS) or amniocentesis. The indication for the fetal sampling procedure (e.g. suspicious ultrasound findings, maternal serum screening results, both parents demonstrated carriers etc).

*Level 3* As for level 2 plus follow up of all pregnancies to confirm the sensitivity and specificity of ultrasound screening.
Objective 6. To link the later outcome in the babies with parental demographic data, to establish the prevalence of genetic disorders which can only be diagnosed after the neonatal period.

Level 0 Omit this objective

Level 1 Arrange for each child in the birth population cohort to be examined at a later interval (for example, when immunisations are done or on admission to nursery school) and to record any structural, genetic or developmental abnormalities found.

3. STUDY SIZE

The target population of mothers and babies studied must be large enough to link social and health data on the parents with the outcome of the present pregnancy. Ideally, the study should focus on all women living within a defined geographical area, whether they have their baby at home or in an institution.

The minimum target population size is 15,000, but a population of up to 50,000 would provide more valuable figures. The size of the study population selected, and the duration of the study, will inevitably differ from one place to another, depending on local circumstances. Some smaller countries may be able to aim for complete national data collection. Others may select a geographical area, such as a health region or district for study. As the study is population-based rather than institution-based, the study team must try to cover as many pregnant women resident in the area as possible, including births at home and those in private and military hospitals which serve the population under study. Failure to include births outside large institutions will cause bias. In countries where almost all births occur in hospitals, a population-based study will also be institution-based. Countries where home births are common may have to use birth registration systems, local health offices, centres or clinics and traditional birth attendants to ascertain which babies are born at home.

4. DATA COLLECTION

Core data will be captured by existing health workers involved in maternal and child health as soon after delivery as possible, as mothers pass through health care and birth registration systems. Data will be collected through a standardized interview with the mother and by standardized examination of each baby.

The health workers involved in the study will require careful training, and in view of staff turnover, regular training and education sessions will be needed. The content of the training should be defined. It is hoped that by using health professionals to record data, awareness of the effect of genetic and congenital anomalies on morbidity and mortality will be strengthened. Health professionals will also gain clinical skills by learning how to examine newborns systematically.

When one of the primary workers suspects a congenital abnormality, the baby should also be examined and the findings recorded by an expert member of the research team.

Local study teams should decide whether the staff who collect the basic data should code information, or whether the data they collect will later be coded by the expert group.

A standardized user-friendly and flexible computer program will be devised for protocol generation and data-entry in each country. Data collection may be computer generated, and "personalized" for the institutions and countries participating.
Data collection is not necessarily limited to that on the standardized forms. Research teams may choose to modify the forms to include additional items of interest to themselves. They will be responsible for recording and analysing any additional data: only the standardized items will be included in the EMRO Mother and Baby Study.

4.1 Collecting data on mothers

The consent of a parent for all objectives of the study which are to be included should be obtained at the time of completing the first data collection form. Each participating mother will be given a unique identifying number.

A target population of at least 15,000 recently delivered women will be interviewed (where possible while in hospital or at a community health office, centre or clinic) to obtain information on their demographic background and obstetric history, using the appended mother’s data collection sheets. It is a priority to include previous stillbirths and deaths to each woman in collected data.

4.2 Collecting blood from the mother

If included in the study, blood samples will be collected from the mother, agreed haematological tests will be conducted, and serum separated, labelled and stored. Blood tests will be carried out according to the methods locally available and chosen by the research team. A discussion of selected methods is included in the manual of operations. It is a priority to ensure quality control.

4.3 Collecting data on babies

Each baby will be given a unique identifying number. This will be the mother’s number plus 1, or in the case of multiple births, 2, 3 etc.

Whether the outcome of the current pregnancy is a live birth or stillbirth, or a neonatal death, the baby will be examined and the findings recorded using a standard check-list for examination of the newborn, on the appended baby data collection sheet 1 (screening examination).

If a congenital anomaly is suspected in a live-born baby the suspicion will be noted, and the baby will be examined by a specialist member of the study team, where available. The findings and provisional diagnosis will be recorded on the appended baby data collection sheet 2 (live baby with congenital anomaly), using the check-list attached.

Special attention should be directed to ensuring that all babies in intensive care are included in the study.
4.4 Collecting data on stillbirths and neonatal deaths

It is a priority to examine all stillbirths and neonatal deaths in the target population.

Wherever possible, each baby that is born dead or dies will be examined by an expert and the observations recorded using baby data collection sheet 3 (stillbirth or neonatal death). Standard photographs and whole body X-rays may be taken, and added to the record. Reports (or copies) of intrauterine, premortem or postmortem ultrasound examinations may be included.

An autopsy will not be feasible in most countries of the EMR but samples may be taken for relevant tests to help diagnosis and provide information on which to base future genetic counselling. These samples may only be taken after a parent has given consent. Samples taken may include: skin biopsy taken within two hours of death for chromosomal analysis; needle biopsy samples; blood samples obtained by cardiac puncture; blood samples from the umbilical cord; placental samples.

If no diagnosis is made, a parent may be asked if such samples can be stored for testing in the future, in the event of further relevant diagnostic tests being discovered.

4.5 Collecting a blood sample from the baby

If included in the study, blood samples from live-born babies will be collected onto clearly marked Guthrie cards, and forwarded to the study centre or designated laboratory for selected investigations. Each Guthrie card will then be sealed into a plastic envelope, and all will be stored in metal boxes in a cool environment, for study later.

When this objective is included in the study, a special effort should be made to include a sample from each dead baby whenever possible: blood may be taken by cardiac puncture.

5. CODING AND ENTRY OF DATA

All records will be forwarded to the study team. They will be checked, coded and entered on the database by staff of the study team. Any uncertainties or incompleteness in data collection will be corrected as soon as possible by liaison with the staff at the place of birth.

Initial coding of mother and infants will use the International statistical classification of diseases and related health problems, 10th edition (ICD10). Where possible, abnormalities found by the study will be coded by specialist doctors undertaking the diagnostic examination. In addition to basic ICD10 coding, they will use McKusick codes, as these are more detailed in recording congenital anomalies than ICD10.

The status of the data will be reviewed at regular meetings of the study team.

6. INITIATING THE STUDY

Within each country a national or local steering group will be convened to consider available country 1 local information on the health burden of congenital and genetic disorders, and to identify priority research areas. Topics considered should include those listed in the introductory document (Regional consultation on standardization of research
*methods related to control of hereditary disorders*), and others that are considered locally relevant.

The steering group will be multidisciplinary. It may include a representative of the Ministry of Health, and specialists in e.g. epidemiology, statistics, paediatrics, genetics, haematology, obstetrics, maternal and child health and primary care, and laboratory specialists in e.g. biochemistry and cytogenetics. Consideration should also be given to including local health service professionals (such as midwives) who will be involved in the day-to-day execution of proposed studies.

The initial task of the steering group is to write a **country report**. The country report should include existing country information, whether published or not, on all the topics listed in the introductory document. It should review the local feasibility and indications for carrying out the Mother and Baby study in whole or in part. Topics to be considered include the following:

- feasibility and desirability of including each study objective;
- necessary target population, and the method and length of study necessary to achieve the desired numbers;
- resources available within the country to assist the study;
- feasibility of assistance to or from other countries within the Region with specific aspects (such as neonatal screening);
- the feasibility and desirability of developing the core study into a prospective longerterm cohort study.

More specific information required may include:

- Any methods of locating place of residence geographically—for example, post codes, province codes;
- Ethnic origins and religions that should be recorded in each country, their distribution in the population and any methods of coding used;
- Languages that should be recorded in each country and any methods of coding used.
- Existing data on place of birth (hospital, home etc), for both urban and rural populations.
- How long women stay in hospital after delivery (precise information in the form of a frequency distribution);
- Existing methods of recording deaths (time limits for stillbirth, perinatal death, infant death etc);
- Feasibility of longer term follow-up of study mothers and babies. This must take account of the fact that babies "lost to follow-up" are likely to include babies who died from congenital or genetic disorders, or have other problems.

If a decision is made to undertake the EMRO Mother and Baby study, a **study team** will be selected to plan, implement and carry out the study. The study team will be small, and able to take executive action to set the study up and run it on a day to day basis. Each country study should be supported by a **small group with computer facilities** to collect, enter, verify and analyse the data.

In smaller countries or local studies, the steering group and study team may be the same, but in larger countries and multicentre studies a management team will be required at each participating centre. Data entry and analysis will usually be centralised at the country level.
7. PILOT STUDIES

Standardized instruments such as the data collection sheets, the manual of operations and the teaching package should be piloted in one or a few countries of the Region, before being recommended for the study.

In each participating country the main Mother and Baby study should be preceded by a pilot study over a set period of time or of a set number of mothers interviewed, e.g. 500. The aim of the country pilot study is to identify and sort out problems in data collection, entry and interpretation.

Coordination and collaboration within the Region through regular study workshops will greatly assist the implementation of studies in different countries.
Table 1:

DIAGNOSIS OF METABOLIC DISORDERS

Notes:

1. Diagnosis of the first affected child in the family depends on biochemical and other laboratory investigations, many of which are not widely available. (A few disorders with common mutations may be diagnosed directly by DNA analysis).

2. Common mutations are not frequent, so that molecular genetic studies are not often used to establish the diagnosis.

3. Once the diagnosis is established, the specific mutation(s) present in the family may be defined by DNA diagnosis. The results are used for prenatal diagnosis for the parents of the first affected child, and for carrier counselling.

4. When the affected child belongs to a large family with multiple consanguineous marriages, and the parents are consanguineous: the chance that the affected child is homozygous is greatly increased, the opportunity to detect other at-risk couples within the family and providing genetic counselling before they have an affected child is greatly increased.

Therefore DNA studies are likely to prove particularly useful for genetic counselling in the Eastern Mediterranean Region.

The above applies for all single gene disorders in populations that favour consanguineous marriage.

Research studies are needed to measure the value of DNA studies for genetic counselling in the Eastern Mediterranean Region.
## SUMMARY OF SELECTED METABOLIC DISORDERS

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance (Incidence in UK)</th>
<th>Gene</th>
<th>Mutations</th>
<th>Treatment/Outcome</th>
<th>Diagnosis</th>
</tr>
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<tbody>
<tr>
<td><strong>Carbohydrate disorders</strong></td>
<td></td>
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<tr>
<td>Glycogen storage disease 1a</td>
<td>AR 1:00 000</td>
<td>Glucose-6-phosphatase</td>
<td>NCM</td>
<td>Treatment: complex</td>
<td>Enz (liver)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome: fair - good</td>
<td></td>
</tr>
<tr>
<td>Galactosaemia</td>
<td>AR 1:4 000</td>
<td>Galactose-1-phosphate uridyl transferase</td>
<td>1 CM 70% alleles</td>
<td>Treatment: fairly easy</td>
<td>Enz</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome: fair</td>
<td></td>
</tr>
<tr>
<td>McArdle disease</td>
<td>AR 1:4 000</td>
<td>Muscle phosphorylase</td>
<td>3 CM 70% alleles</td>
<td>Treatment: difficult</td>
<td>Enz (muscle)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome: moderate</td>
<td></td>
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<tr>
<td><strong>Aminoacid disorders</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Phenylketonuria</td>
<td>AR 1:4 000</td>
<td>Phenylalanine lydroxylase</td>
<td>&gt;60</td>
<td>Treatment: difficult</td>
<td>PAA</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome: fair - good</td>
<td></td>
</tr>
<tr>
<td>Tyrosinaemia type 1</td>
<td>AR 1:0 000</td>
<td>Fumarylacetoacetase</td>
<td>NCM</td>
<td>Treatment: complex + expensive</td>
<td>UOA</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Enz</td>
</tr>
<tr>
<td>Carbamylphosphate synthetase deficiency</td>
<td>AR &gt;1:200 000</td>
<td>Carbamylphosphate synthetase deficiency</td>
<td>NCM</td>
<td>Treatment: difficult</td>
<td>PAA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome: poor</td>
<td>UPYR Enz (liver)</td>
</tr>
<tr>
<td>Ornithine carbamyl transferase deficiency</td>
<td>X-linked 1:5 000</td>
<td>Ornithine carbamyl transferase deficiency</td>
<td>NCM</td>
<td>Treatment: difficult</td>
<td>PAA</td>
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<td></td>
<td></td>
<td>Outcome: poor - good</td>
<td>UPYR Enz (liver)</td>
</tr>
<tr>
<td>Citrullinaemia</td>
<td>AR 1:50 000</td>
<td>Argininosuccinate synthetase deficiency</td>
<td>NCM</td>
<td>Treatment: difficult</td>
<td>PAA</td>
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<td></td>
<td>Outcome: poor - good</td>
<td>UPYR Enz (liver)</td>
</tr>
<tr>
<td>Maple syrup urine disease</td>
<td>AR 1:250 000</td>
<td>Branch chain ketoacid dehydrogenase</td>
<td>NCM</td>
<td>Treatment: very complex</td>
<td>PAA</td>
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<td></td>
<td></td>
<td>Outcome: poor - good</td>
<td>(Enz)</td>
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<tr>
<td>Homocystinuria</td>
<td>AR 1:250 000</td>
<td>Cystathione-β-synthase</td>
<td>NCM</td>
<td>Treatment: fairly easy</td>
<td>PAA, UAA</td>
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<td></td>
<td></td>
<td>Outcome: poor - good</td>
<td></td>
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<tr>
<td>Non ketotic hyperglycinaemia</td>
<td>AR 1:100 000</td>
<td>Glycine cleavage enzyme</td>
<td>NCM</td>
<td>Treatment: none</td>
<td>PAA, CS²AA</td>
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<td></td>
<td></td>
<td>Outcome: very poor</td>
<td>Enz (liver)</td>
</tr>
<tr>
<td>Disorder</td>
<td>Inheritance (Incidence in UK)</td>
<td>Gene</td>
<td>Mutations</td>
<td>Treatment/Outcome</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>--------------------------------</td>
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</tr>
<tr>
<td><strong>Organic acidemias</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Methylmalonic acidemia</td>
<td>AR 1:50000</td>
<td>Methylmalonyl CoA mutase</td>
<td>NCM</td>
<td>Treatment: (easy) - difficult</td>
<td>UOA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome: good - v. poor</td>
<td></td>
</tr>
<tr>
<td>Propionic acidemia</td>
<td>AR 1:80000</td>
<td>Propionyl CoA carboxylase</td>
<td>NCM</td>
<td>Treatment: (easy) - difficult</td>
<td>UOA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome: good - v. poor</td>
<td></td>
</tr>
<tr>
<td>Isovaleric acidemia</td>
<td>AR 1:100 000</td>
<td>Isovaleryl CoA dehydrogenase</td>
<td>NCM</td>
<td>Treatment: fair</td>
<td>UOA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome: fair - good</td>
<td></td>
</tr>
<tr>
<td><strong>Disorders of fatty acid oxidation</strong></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Medium chain acyl CoA dehydrogenase def</td>
<td>AR 1:10000</td>
<td>Medium chain acyl CoA dehydrogenase</td>
<td>ICM = 90% alleles</td>
<td>Treatment: straightforward</td>
<td>UOAs/BAC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Good with early diagnosis</td>
<td>DNA</td>
</tr>
<tr>
<td>Trifunctional enzyme def</td>
<td>AR 1:80000</td>
<td>Trifunctional enzyme</td>
<td>ICM = 80% alleles</td>
<td>Treatment: difficult</td>
<td>UOAs/BAC/DNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Good with early diagnosis</td>
<td></td>
</tr>
<tr>
<td>Very long chain acyl CoA dehydrogenase def</td>
<td>AR 1:100 000</td>
<td>Very long chain acyl CoA dehydrogenase</td>
<td>NCM</td>
<td>Treatment: difficult</td>
<td>Good with early diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Good with early diagnosis</td>
<td></td>
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<tr>
<td><strong>Lipid disorders</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Familial hypercholesterolaemia</td>
<td>AD 1:500</td>
<td>LDL receptor</td>
<td>&gt;1000</td>
<td>Homozygote: poor</td>
<td>Lipid analyses</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Heterozygote: not clear</td>
<td></td>
</tr>
<tr>
<td>Disorder</td>
<td>Gene</td>
<td>Diagnosis</td>
<td>Treatment/Outcome</td>
<td>Inheritance (incidence in UK)</td>
<td></td>
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<tr>
<td>--------------------------</td>
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<td>-------------------</td>
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<td></td>
</tr>
<tr>
<td>Acid maltase deficiency</td>
<td>Acidmaltase</td>
<td>Sp inv</td>
<td>Treatment: poor</td>
<td>AL 1:100,000</td>
<td></td>
</tr>
<tr>
<td>( Pompe disease)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gaucher disease</td>
<td>Glucerebrosidase</td>
<td>Sp inv</td>
<td>Treatment: very expensive in UK</td>
<td>AL 1:40,000</td>
<td></td>
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<td>Metachromatic leucodystrophy</td>
<td>Arylsulphatase A</td>
<td>SP inv</td>
<td>Treatment: experimental in UK</td>
<td>AL 1:50,000</td>
<td></td>
</tr>
<tr>
<td>Tay Sachs disease</td>
<td>Hexosaminidase A</td>
<td>SP inv</td>
<td>Outcome: poor</td>
<td>&gt;1,250,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment: none</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropoly saccharidases</td>
<td>NPS I (Hunter)</td>
<td>UOA A B C D E  DNA</td>
<td>Treatment: experimental</td>
<td>2 CM in UK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NPS II (Hunter)</td>
<td>UGA A B C D E  DNA</td>
<td>Outcome: poor</td>
<td>2 CM in UK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NPS III (Sanfilippo A, B, C, D)</td>
<td>UGA A B C D E  DNA</td>
<td>Treatment: experimental</td>
<td>2 CM in UK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NPS IV (Mouquo A)</td>
<td>UGA A B C D E  DNA</td>
<td>Outcome: poor</td>
<td>3 CM in UK</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment: none</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Symptomatic treatment of complications is beneficial.
### Abbreviations

<table>
<thead>
<tr>
<th>MUTATIONS</th>
<th>INVESTIGATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CM</td>
<td>Blood acylcarnitines</td>
</tr>
<tr>
<td>NCM</td>
<td>Cerebrospinal fluid amino acids</td>
</tr>
<tr>
<td></td>
<td>Molecular genetic studies</td>
</tr>
<tr>
<td></td>
<td>Enzyme assays</td>
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<tr>
<td></td>
<td>Plasma amino acids</td>
</tr>
<tr>
<td></td>
<td>Special investigations, e.g. bone marrow, etc.</td>
</tr>
<tr>
<td></td>
<td>Urine amino acids</td>
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<tr>
<td></td>
<td>Urine glycosaminoglycans</td>
</tr>
<tr>
<td></td>
<td>Urine organic acids</td>
</tr>
<tr>
<td></td>
<td>Urine pyrimidines</td>
</tr>
</tbody>
</table>

#### MUTATIONS
- CM: Common mutation
- NCM: No common mutation

#### INVESTIGATIONS
- BAC: Blood acylcarnitines
- CSFAA: Cerebrospinal fluid amino acids
- DNA: Molecular genetic studies
- Enz: Enzyme assays
- PAA: Plasma amino acids
- Sp Inv: Special investigations, e.g. bone marrow, etc.
- UAA: Urine amino acids
- UGAGs: Urine glycosaminoglycans
- UOA: Urine organic acids
- UPYR: Urine pyrimidines
DRAFT DATA COLLECTION SHEETS FOR MOTHER AND BABY

Note. These data collection sheets are drafts, reproduced here to show the type of data collection that is proposed. The draft protocol permits considerable flexibility. For example, items in italics in the following sheets apply only when a named follow-up study has been chosen, rather than an anonymous epidemiological study. Other optional items are indicated where they arise.
MOTHER’S DATA COLLECTION SHEET 1: DEMOGRAPHIC DATA

Identification
Country code (Computer generated)
Code/Name of Institution (Computer generated)
Medical record number (Computer generated)
Serial number (Computer generated)
Mother’s ID No: .................................. (unique identifier, e.g social security number)
Mother’s consent for epidemiological study (if needed)  YES/NO
Mother’s consent for named follow-up study (if needed)  YES/NO

Mother’s Name: ......................................

Mother’s date of birth: dd/mm/yy or age in years now............................ estimate/certain
Mother’s address: Area
City/village
Province number or other geographic code street and house number telephone no
Address if different a year ago (area, city/village, street and house no)
Primary Health Care Unit attended in this pregnancy.................................
Date and time of delivery of this baby dd/mm/yy at 00.00 (24 hour clock)

Details obtained by interview
Date and time of interview: dd/mm/yy at 00.00 (24 hour clock)

Father’s Name: ......................................

Father’s date of birth: dd/mm/yy: or age in years now ..........estimate/certain: or age unknown
Mother’s age at marriage to this husband (years) ......................................

Mother-tongue (include unknown)
Years of formal education (include unknown)
Able to read - Yes/No/ Unknown
(if any doubt ask mother to read a standard letter)
Occupation (include unknown)
Industry worked in (include unknown)
<table>
<thead>
<tr>
<th>Pregnancy No</th>
<th>Abortn / SB</th>
<th>LB</th>
<th>IF DEAD</th>
<th>IF ALIVE</th>
<th>Any abnormalities</th>
<th>IF UNWELL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>mo</td>
<td>cause</td>
<td>mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>died</td>
<td>Cause of death</td>
<td>Age years</td>
<td>General Condition</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;1 mo, 1 mc-1 yr, &gt; 1 yr</td>
<td>Well Unwell</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>&lt;1 mo, 1 mc-1 yr, &gt; 1 yr</td>
<td>Well Unwell</td>
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<td>&lt;1 mo, 1 mc-1 yr, &gt; 1 yr</td>
<td>Well Unwell</td>
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<td>&lt;1 mo, 1 mc-1 yr, &gt; 1 yr</td>
<td>Well Unwell</td>
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<td>&lt;1 mo, 1 mc-1 yr, &gt; 1 yr</td>
<td>Well Unwell</td>
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<td></td>
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<td>&lt;1 mo, 1 mc-1 yr, &gt; 1 yr</td>
<td>Well Unwell</td>
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<td></td>
<td></td>
<td></td>
<td>&lt;1 mo, 1 mo-1 yr, &gt; 1 yr</td>
<td>Well Unwell</td>
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<td></td>
<td>&lt;1 mo, 1 mo-1 yr, &gt; 1 yr</td>
<td>Well Unwell</td>
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<td></td>
<td></td>
<td></td>
<td>&lt;1 mo, 1 mo-1 yr, &gt; 1 yr</td>
<td>Well Unwell</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;1 mo, 1 mo-1 yr, &gt; 1 yr</td>
<td>Well Unwell</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional comments
MOTHER'S DATA COLLECTION SHEET 3: PARENTAL CONSANGUINITY

The health worker will address the following questions to the mother. Both questions I & II will be asked.

I. Is your husband related to you on your father's side?  
   - Yes  No  
   If no, go to next section  
   If yes, is he:  your father's brother's son?  
   - Yes  No  
   your father's sister's son?  
   - Yes  No  
   If no, ask specifically about the relationship

II. Is your husband related to you on your mother's side?  
   - Yes  No  
   If no, go to the next section  
   If yes, is he:  your mother's brother's son?  
   - Yes  No  
   your mother's sister's son?  
   - Yes  No  
   If no, ask about specific relationship

The health worker will then ask whether the woman's parents are related, in the same way:

I. Is your father related to your mother on her father's side?  
   - Yes  No  
   If no, go to next section  
   If yes, is he:  her father's brother's son?  
   - Yes  No  
   her father's sister's son?  
   - Yes  No  
   If no, ask specifically about the relationship

II. Is your father related to your mother on her mother's side?  
   - Yes  No  
   If no, go to the next section  
   If yes, is he:  your mother's brother's son?  
   - Yes  No  
   your mother's sister's son?  
   - Yes  No  
   If no, ask about specific relationship

The health worker will then ask whether the woman was married before. Yes No  
If yes, she will ask how the woman was related to her previous husband

I. Was your previous husband related to you on your father's side?  
   - Yes  No  
   If no, go to next section  
   If yes, was he:  your father's brother's son?  
   - Yes  No  
   your father's sister's son?  
   - Yes  No  
   If no, ask specifically about the relationship

II. Was your previous husband related to you on your mother's side?  
   - Yes  No  
   If no, go to the next section  
   If yes, was he:  your mother's brother's son?  
   - Yes  No  
   your mother's sister's son?  
   - Yes  No  
   If no, ask about specific relationship
MOTHER'S DATA COLLECTION SHEET 4: THIS PREGNANCY

Month of gestation when antenatal care started
1 2 3 4 5 6 7 8 9 gestation unknown No care
If antenatal care given, who gave it?
Traditional birth attendant, health worker, doctor, other please specify
Mode of delivery (normal, vaginal breech, forceps or suction, caesarean)
Best estimate of gestational age of baby in weeks

Maternal illness:
Diabetes yes / no / unknown If yes: insulin dependent / non-insulin dependent / gestational
Epilepsy yes / no / unknown If yes: was there drug treatment in pregnancy? yes / no / unknown
Other illnesses (see check list) yes / no / unknown If yes - specify

Maternal infections yes / no / unknown
Maternal therapy yes / no / unknown

Family history of genetic or handicapping disorder? (Check-list as for obstetric history)
Yes / no / unknown (if yes, draw family tree according to separate protocol)

Mother's blood group: / unknown isoimmunised yes / no / unknown
Father's blood group: / unknown

Haemoglobin disorders known carrier?: diagnosis
Mother
Father

Maternal cigarette smoking in this pregnancy
Any cigarettes smoked in this pregnancy? yes / no / unknown
If yes, estimate number of cigarettes smoked per day ................................................../ day

Optional: Maternal alcohol intake in pregnancy: Occasional (1 drink/week) regular drinker / unknown

Social data:
Ethnic origin (check list, including unknown: country generated)
Religion (check list, including unknown: country generated)

Maternal blood sample sent to laboratory yes / no / unknown / permission refused

Signature of health worker who interviewed mother
.................................................................
BABY DATA COLLECTION SHEET 1: SCREENING EXAMINATION

Mother's Name: ................................................................. Unknown
Baby serial No. = mother's serial no, with /1 (computer generated)
In case of multiple births, spare sheets are filled in with mother's number /2, /3 etc.
Live birth / stillbirth / neonatal death (age at death in hours)

PHYSICAL EXAMINATION
Date of examination dd/mm/yy
Date of birth of baby dd/mm/yy unknown
Are there any obvious abnormalities on looking at the baby?
If yes, please specify
Sex: male/female/undetermined
Birth weight (kg): ........................................../ not weighed
Length: Crown heel in cms ................../ not measured Optional - see protocol
Head circumference in cms: / not measured
(Needs appropriate cut off points for referral to specialist)

General condition of baby
good ?? sick
Colour (pallor, cyanosis etc.) and respiration
good ?? sick
Activity (sucking, moving limbs, tonus, crying)
good ?? sick
Jaundice yes/no
Meconium passed yes/ no

Baby front: abnormality? Yes No Specialist's comments and diagnosis
Scalp defects
Ears deformity
pre-auricular tags or pits
Eye abnormalities
Nose abnormalities
Hare-lip
Cleft palate
Neck: sinuses, abnormal swellings
Chest: deformity
Abdomen: marked abnormality
Genitalia: Male: penis - hypospadias
Right testis descended/left testis descended
hydrocele
Genitalia: Female: normal/abnormal
Genitalia: Ambiguous
## Baby back: Abnormality?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
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</thead>
</table>

### Specialist's comments and diagnosis

#### Skull defects

#### Spine defects

#### Sacral abnormality

<table>
<thead>
<tr>
<th>sinus</th>
<th>hair tuft</th>
</tr>
</thead>
</table>

#### Extremities

<table>
<thead>
<tr>
<th>Abnormality of arm</th>
<th>R</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormality of hand</td>
<td>R</td>
<td>L</td>
</tr>
<tr>
<td>Abnormality of leg</td>
<td>R</td>
<td>L</td>
</tr>
<tr>
<td>Abnormality of foot</td>
<td>R</td>
<td>L</td>
</tr>
</tbody>
</table>

#### Talipes

Joints: restriction of elbow(s) / restriction of kncc(s)

#### Skin

Skin haemangiomas
- hyper or hypopigmentation
- abnormality of skin texture
- oedema

#### Tone

- hypotonia
- Moro reflex: normal / abnormal

#### Paralysis of any limbs

#### Additional comments (free field)

- Guthrie spot taken: yes / no / permission refused
- Baby referred for specialist examination: yes / no

If referred, name of person to whom baby referred

### Signature of health worker who examined baby

..................................................................................................................................................
BABY DATA COLLECTION SHEET 2: SPECIALIST EXAMINATION

Mother's name:................................................. Baby ID no:...................
Date of Birth: dd/mm/yy

LIVE BAY WITH CONGENITAL ABNORMALITY

Name of examining doctor: ....................................................................

Ultrasound scan conducted during pregnancy? yes/ no  seen yes / no
Photograph        yes / no / permission refused
X-rays of relevant parts yes / no
Ultrasound scan    yes / no
Screen for CMV, rubella and toxoplasmosis taken yes/ no

Attach report of ultrasound examinations (prenatal and post-natal) and X-rays, and pictures where possible

Provisional diagnosis

Signature of specialist who examined baby .................................................................

STILLBIRTH OR NEONATAL DEATH

Consent given for examination  yes / no / permission refused
Name of examining doctor: ............................................................

Ultrasound scan conducted during pregnancy: yes / no.  seen yes / no
Photograph of dead baby     yes / no / permission refused
X-rays: whole body          yes / no / permission refused
Autopsy                     yes / no / permission refused
                         Full       yes / no / permission refused
                         Limited     yes / no / permission refused
Screen for CMV, rubella and toxoplasmosis taken yes / no / permission refused
Attach report of autopsy examination, ultrasound, pictures and X-rays, where possible

Provisional diagnosis

Signature of specialist who examined baby .................................................................
DRAFT MANUAL OF OPERATIONS

(very preliminary version)
INSTRUCTIONS FOR COMPLETING THE FORMS

Standard WHO data forms will be provided on diskette to country teams, and forms will be customised and printed locally. (May need to be in local language, in view of personnel collecting the data?)

The questionnaire should be administered to the mother in privacy by a trained attendant, at a time when she is rested and at leisure.

Selection of participants
All women delivering in the selected institution or geographical area will be invited to join the study. If this is not possible, participants must be selected in a way that ensures they form a random sample, e.g. those delivering on certain days of the week.

Consent
All participants must give consent to join the study. If consent is refused the mother's wish must be respected. (But what if a mother who refuses consent has a malformed baby or stillbirth? Probably pregnancy outcome should be recorded in any case)

Identifiers

Epidemiological study
Country code, institution code (when the study is hospital based) and mother's serial number are the necessary identifiers.
When the study is community-based, identifiers should include postcode or equivalent.

Follow-up study
If a follow-up study is selected, identifiers must include exact name and address of the mother, and any other details necessary to ensure follow-up of the baby. A key element in ensuring effective follow-up in other long-term studies (e.g. the UK birth cohort studies) has been to send the parents/child a birthday card every year, with a request to reply, and reminder to report any change of address. (This incidentally provides an opportunity to test mothers' reading ability when there is any doubt, by asking the mother to read an example of a follow-up letter.)

Use of existing hospital notes
Study workers may take data from existing notes (this may speed parts of the questionnaire up), but should check the data with the mother in the course of the interview. Use of the notes will allow entry of data such as mother's Rh and other blood groups, isoimmunization etc.
MOTHER'S DATA COLLECTION SHEET 1

Country code
The official WHO country code will be printed on forms produced locally.

Institution code (or name)
This should appear on customised country forms printed locally.

Serial numbers.
Each mother's computer-generated serial number will be unique in each country.
Each mother's form will have a correspondingly-numbered baby's form attached.
In case of multiple births a new unnumbered baby form must be produced, and numbered, by
the interviewer (see below for coding of baby forms).

Mother's ID number
In many countries adults have a unique social security number that allows them to be
identified reliably. For follow-up studies such an identifier should be recorded.

Consent
This could be quite difficult, as many mothers may feel unable to give consent unless they
have first discussed it with their husbands.
For an epidemiological study, some participants favoured simply informing the mother that
the study is taking place. If consent is refused, should mother's form finish here, or should
outcome of this pregnancy be reported (to ensure extent of bias if any)?
Parents' consent and information for the parents will definitely be needed for a follow-up
study. Experience will be needed.

Parents' names.
Mother's and father's names are always recorded on the data collection sheets. They are
entered in the computer only for a named study.

Mother's date of birth
Day/month/year e.g. 01 01 66. This will not always be known. In this case an approximation
should be obtained (may be based on year of marriage in some cases).

Address
Will be entered on form, but not on computer (except for a named study).
Discuss availability of postcodes or similar. in tracing families for follow-up studies.
Telephone number will not be recorded, except for a follow-up study.

Primary health care unit attended in this pregnancy
Necessary for a follow-up study.

Date and time of this baby's birth. Day, month, year. (e.g. 01 08 96)
Time of birth. 24 hour clock. Hour, minutes. e.g. 0850. or 2310.
It is essential to enter time, for interpretation of Guthrie results.

Date and time of interview. Record as above.
Age at marriage to this husband: years
May be the most reliable indicator of maternal age in some cases. Though divorce is uncommon, widowhood is not.

A check-list is needed for each country. It must include "none" and "unknown". Harmonization may be achieved at first WHO workshop.

Years of formal education.
Record separately for mother and father
Code 0 - however many years of education.

Able to read?
It may be advisable to check the mother's literacy, especially if a long-term follow-up study is contemplated. This may be done by asking her to check a standard letter of the kind that may be sent to her to maintain contact.

Occupation
Record separately for mother and father
Actual occupation be entered, and coded by the team. Note: if occupation entered, e.g. ("army" is not enough: an indication of rank is required. (Or is it, in view of information on education?) If the mother does not work outside the home, "housewife" should be entered.

Industry worked in (for risk of exposure to toxic chemicals).
MOTHER'S DATA COLLECTION SHEET 2: OBSTETRIC HISTORY

We considered asking about miscarriage, whether induced or not, but excluded it because we did not expect to obtain reliable data. However, in some circumstances the replies might be reliable. In this situation the question might be included as a local substudy.

If there has been more than one partner, draw a line across the chart at the appropriate point and indicate (Partner 1, partner 2 etc.).

Any abnormality (in previous pregnancy) - specify - CHECK-LIST. Use the following categories:
- physical abnormality
- mental handicap
- blindness
- deafness
- inherited disease (thalassaemia, sickle cell haemophilia, etc.)
- developmental delay
- other

Enter precise diagnosis when the mother knows one.

MOTHER'S DATA COLLECTION SHEET 3: PARENTAL CONSANGUINITY

This still needs some work, to help researchers record relationships other than 1st cousins correctly. A list of local terms in the local language is needed.

MOTHER'S DATA COLLECTION SHEET 4: THIS PREGNANCY

antenatal care and mode of delivery
self-explanatory

Maternal illness
Maternal illness. Other illness? - CHECK LIST Pre-eclampsia / eclampsia, bleeding, needing transfusion, obstructed labour
Prolonged labour (> how many hours?)

Maternal infections
We considered this at length and decided no useful or reliable list could be made. Any information from mother or notes should be recorded.

Maternal therapy
Though we also doubted the value of recording this, it was concluded that any unusual drug treatment should be recorded.

Parents' blood groups
This, and details of isoinmunization and father's Rh group must be taken from (or at least checked in) the obstetric notes. If minor groups are tested for, they may be included.

Family history of genetic or handicapping disorder?
**Maternal and paternal haemoglobinopathy status**
Complete from notes, and also ask woman
There follow questions that may be delicate. These are asked last, and in some countries it may be inappropriate to ask them.

**Maternal cigarette smoking in pregnancy**
In estimated number of cigarettes smoked per day. May be calculated from number of packets per week etc.

**Alcohol consumption during pregnancy**
Optional

**Ethnic group**
Ethnic group must be entered separately for mother and father.
A check-list is needed, generated by each country team. It must include "unknown".
Harmonization of coding may be achieved at first WHO workshop.

**Religion**
This is an optional question, as it may be delicate in some countries.
Religion must be entered separately for mother and father.

**Maternal blood sample sent to laboratory**
BABY DATA COLLECTION SHEET 1  SCREENING EXAMINATION

All live and stillborn babies in the study population should have a standard physical examination. The protocol leaves room to expand the physical examination, depending on the expertise of the examiner.

Note. For babies in intensive care, the examination must be done by the doctor.

The examiner must have:
- a good torch,
- a proper tape-measure,
- a good tongue depressor.

**Length** (optional, as not all participants were convinced of its reliability).
Measured either using a stadiometer, or as follows.
Two people are needed. One lies the baby with its head against an upright, and extends the legs. The second uses a tape-measure to measure the baby's length along the surface (not on the baby).
Doing this requires a teaching package or video teaching method.

**Physical examination.**
All rows in this part of the questionnaire should be completed.

*(Note - need to explain why congenital dislocation of the hip is not included in the physical examination)*

**General impressions** are recorded first

**Detailed examination**
The (nonspecialist) conducting the first examination should tick in "yes" or "no" for each item. When an abnormality is suspected the baby should be examined by a specialist, who makes fuller comments in the final column.

Minor peculiarities should not be recorded. The following is an indication of the order of abnormalities to be reported.

- Ear deformity (not rotation or simplification of pattern)
- Eye abnormalities (absence of eyeball, microphthalmia, irregularity of pupil (both eyes must be examined with a torch)
- Nose abnormality (e.g. bifid nose, absent nares)
- Cleft palate (look with tongue-depressor and torch)
- Abdomen (Biblical hernia, omphalocele, gastroschisis, bladder extrophy)
- Abnormality of hand: polydactyly
  - syndactyly
  - absence of digits
  - absence of nails
- Skin hyper or hypo pigmentation - 1 cm diameter or more
- Abnormality of skin texture: e.g. epidermolysis bullosa, or colloidion baby

Exclusions are listed in the Appendix
Note. In a community-based study, deceased babies will not reach an expert for examination. Therefore participating health workers should carry a camera if possible.

BABY DATA COLLECTION SHEET 2: SPECIALIST EXAMINATION

Should be completed in all cases with an abnormality (part 1 of the form), and for all dead babies (part 2 of the form).

Live baby. A note is made of examinations, including ultrasound during pregnancy. Reports are attached when possible.

Stillbirth or neonatal death.

Photographs of (dead) baby:
  whole body (front and back),
  AP and lateral views of head and neck
  close-up of specific abnormalities

Report of postmortem examination, photograph, ultrasound and X-ray pictures should be attached to the reporting form.
EXCLUSIONS OF MINOR ANOMALIES AND CONDITIONS NOT CONSIDERED TO BE MALFORMATIONS

These anomalies will be reported to specialists for exclusion of syndromes, but will not be reported by the specialist to the main study.

**Minor anomalies**

- Spina bifida occulta - uncomplicated
- Stenosis or stricture of lacrimal duct
- Anomalies of ear - minor or unspecified
- Anomalies of nose - minor or unspecified
- Deformity of face - minor or unspecified
- Anomalies of nipple - minor, for example accessory nipple
- Congenital umbilical hernia
  - inguinal hernia
  - paraumbilical hernia
- Undescended testicle
- Ectopic testicle
- Congenital hydrocele or hydrocele of testis
- Glandular hypospadias - if meatus lies before coronary sulcus
- Abnormal palmar crease
- Skin anomaly - surface less than 4 cm: skin tag, naevus, angioma, haemangioma, glomus tumour, lymphangioma, birthmark
- Clicking hip - unless confirmed as dislocatable
- Clubfoot of positional origin
- Anomalies of toes - minor or unspecified such as hallux valgus, hallux varus or "orteil en marteau"
- Cardiac murmur - functional or unspecified
- Anomaly of umbilical artery - absence or hypoplasia, single umbilical artery

(Source: EUROCAT)

**Conditions not considered to be malformations**

- Abdominal distension
- Abnormality - blood group
- Acidaemia - organic
- Atelectasis
- Australia antigen
- Bruising splenic region
- Cephalohaematoma
- Cerebral palsy
- Cyst on cord
- Deafness, congenital
- Dystocia, shoulder
- Haematoma
- Haematoma, umbilical cord
- Hyaline membrane disease
- Hyperventilation
- Intrauterine growth retardation
Meconium liquor
Meconium peritonitis
Necrotizing enterocolitis
Palsy of facial nerve - traumatic
Perforated gut
Phimosis
Pleural effusions
Polycythaemia
Respiratory distress syndrome
Ruptured bowel
Sclerema
Two teeth or congenital teeth
Umbilical granuloma
Weak femoral pulses
(Adapted from EUROCAT)
DRAFT PROTOCOLS FOR THE OPTIONAL COMPONENTS OF THE MOTHER AND BABY STUDY
1. OPTIONAL STUDY OF MATERNAL BLOOD SAMPLES (OBJECTIVE 3)

Blood will be taken from all mothers, and tested for haemoglobin disorders and iron deficiency (using methods independent of Hb level such as serum iron or ferritin level, or the far simpler method of haemato fluorimetry).

Maternal serum may be stored and tested anonymously in the future in batches, for epidemiological studies of e.g.

- Antibody to teratogenic maternal infections such as rubella, toxoplasma and syphilis, and to other infections relevant to maternal health such as chlamydia, trachoma, herpes virus and other sexually transmitted diseases.
- hepatitis B antigen (data already available?)
- vitamin A levels
- white cell folate
- ferritin

2. OPTIONAL STUDY OF BABY BLOOD SAMPLES (OBJECTIVE 4)

Blood spots should be taken from all babies onto Guthrie cards by a trained health worker.

Ease of obtaining optimal samples and the tests selected will depend on the pattern of care at delivery in each country. Timing of taking blood spots may be an important problem. Blood spots taken immediately after birth are suitable for screening for e.g. abnormal haemoglobins, G6PD deficiency, congenital hypothyroidism and DNA analysis. However, screening for PKU, some other metabolic disorders and cystic fibrosis requires a blood sample taken more than 48 hrs, and ideally about 5 days after birth. If it is intended to screen for these disorders, there may be a problem in collection where babies are discharged early. The exact date and time of sampling must be recorded on every Guthrie form.

Samples will be taken by aseptic heel prick. Health workers may consider analgesia for the baby by giving drops of 50% sucrose orally just before heel-prick.

Take six blood spots by heel-prick onto labelled Whatman 3m filter paper (in a named follow-up study two spots may be kept with the baby’s record).

Consider how cards are to be transported to the study team or laboratory.

Store sealed in plastic envelopes. (Stored Guthrie cards will keep for 5–20 years if kept in metal boxes to exclude mice etc., in a cool environment).

Ideally the samples should be tested for the conditions listed below. Some of these tests may be available in some countries, but it is unlikely that all will be available in any country. Therefore each country team needs to plan which tests will be carried out as soon as samples

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become available, which can be tested for with help from other laboratories in the Region, and which should be planned for the future on stored samples.

Immediate tests may be possible for: PKU (microbiological); CHT (radioimunoassay) (this will also relevant to for assessing iodine deficiency); abnormal haemoglobins; G6PD deficiency; cystic fibrosis; Duchenne muscular dystrophy.

Stored samples may be available for later testing e.g. (in a named study) in case a child dies and a genetic disorder is suspected, and for future epidemiological studies of conditions such as galactosaemia, fragile X syndrome, congenital adrenal hyperplasia, myotonic dystrophy, LDL receptor defects etc.

3. OPTIONAL STUDY ON PRENATAL DIAGNOSIS (OBJECTIVE 5)

Aim
To establish the frequency of antenatally diagnosed congenital anomalies in the study population.

Background
Since ultrasound examination is a widespread practice in modern obstetrics, increasing numbers of fetal anomalies are being diagnosed antenatally at various stages of pregnancy. Diagnosis is made either through specific programmes designed to diagnose structural malformations and chromosomal markers, or incidentally when scanning the fetus for gestational age and growth rate. Significant numbers of such pregnancies do not reach a stage of viability. Studying only the birth prevalence of congenital anomalies will significantly underestimate their prevalence in pregnancy, and lead to underestimation of mortality and morbidity due to congenital and genetic disorders.

Objectives
- To identify fetal anomalies that are diagnosed prenatally and to include them in the overall results for the study population.
- To evaluate the sensitivity, specificity and overall quality of ultrasound services in the prenatal diagnosis of fetal anomalies.

Method
All pregnant women enrolled in the study population will be referred for ultrasound examination between 16 and 18 weeks gestation.

If an anomaly is suspected, it will be reported to the consultant obstetrician in the study team for advice and management. It must be emphasised that the suspicion of fetal anomaly found on scan should not alter the standard management of the maternity unit. The outcome of the pregnancy will be followed and recorded.

Whether the baby is born alive or dead, the standard interview and examination for the study will be undertaken by a health worker, with referral to a specialist member of the study team to confirm the anomaly and make a detailed diagnosis for comparison with the ultrasound findings.
In the case of abortion, the abortus will be examined by a specialist and tissue samples and photographs will be taken (after the consent of a parent has been obtained) for diagnosis to inform future genetic counselling.
ADDITIONAL STUDIES FOR WHICH PROTOCOLS MAY BE DEVELOPED

1. COMMON CONGENITAL ABNORMALITIES, NOT READILY DIAGNOSED AT BIRTH

Congenital heart disease

Most significant cases will present before 2 years of age, and may lead to death or to referral. An idea of frequency may be obtained from cardiologists, and cardiac surgeons. Are there specialist paediatric cardiac surgeons in the country? Where do cardiac surgeons obtain cases from e.g. capital city, or whole country? How many children have they operated on in the past 2 years?

Data to collect
Name/number of child, date of birth, place of origin, cardiac abnormality, operation performed, outcome.

Mental handicap

- how to identify mentally handicapped children and proceed to a diagnosis.
- how to reach an estimate of the proportion of mental handicap that might be avoided.

In order to begin, what questions should be answered, e.g.
Are there institutions for the mentally handicapped?
What proportion of patients attend them?

Data to collect
Name/number of child, date of birth, IQ, provisional diagnosis.

Impairment of vision and hearing

A WHO protocol for blindness already exists - the WHO/PBL eye examination record for children with blindness and low vision. A similar protocol for deafness would be valuable.

What data should be collected?
Are there institutions for the blind or deaf?
What proportion of patients attend them?

Data to collect
Name/number of child, date of birth, degree of impairment, provisional diagnosis.

2. REGISTERS OF COMMON HEREDITARY DISORDERS

Down syndrome: what minimal data should be included in a register?
Is chromosomal diagnosis available? If yes, laboratory records will be invaluable.
Is there a register of Down children?
What proportion of Downs are known?

Minimal data to collect
Name/age of child, date of birth
Maternal age at birth
Other affected siblings?

Thalassaemia, sickle cell disorders, haemophilia
What proportion of cases are detected and treated?
How many centres treat them?

Minimal data to collect
Name/number of child, date of birth, diagnosis, residence, origin, parental consanguinity?
SURVEY OF THE IMPACT OF INHERITED DISEASE ON THE FAMILY

Study disorders: thalassaemia, sickle cell disorders, haemophilia (selected because they are common) are present in most EMR countries, and many patients attend specialist treatment centres regularly.

We visualize a confidential interview of the mother (ideally at home but more likely in the clinic). The interviewer should be a woman. The atmosphere should be sympathetic, and emphatically non-directive.

Mother's age, age at marriage, parental consanguinity (protocol of Mother and Baby study).

Obstetric history (protocol of Mother and Baby study)
Table of each pregnancy,
year of pregnancy, outcome, affected children, childhood deaths etc.

Utilization of family planning:
year started, method -- abstention, withdrawal, condom, diaphragm, IUD, Depo-Provera, pill.

How many siblings has the mother? (draw family tree).

For each sibling:
• how many children?
• how many deaths in infancy?
• any with the same condition?

How many siblings has the father? (Number of sisters and brothers).
Have any got children with the same condition?

Controls
Select two controls for the mother. Controls should be the mother's siblings.
The mother should be asked to give, as far as possible, the above obstetric and family planning history for two siblings, selected in the following order of preference.

Two older sisters
One older, one younger sister
Two younger sisters
One each older sister and brother
One each older and younger sister and brother
One each younger sister and brother.
If the woman has no sisters, select brothers in the same order.
If the woman has only one sibling, take the reproductive history of that sibling
If the woman has no siblings, there can be no control.

Knowledge and understanding
Questionnaire to elicit details of the following:
Mother's awareness of the inheritance of the disorder.
Understanding of her carrier status. Significance for herself, and for her siblings. Awareness of the possibility of prenatal diagnosis, and the option of termination of pregnancy.
ANNEX 1

LIST OF PARTICIPANTS

EGYPT

Professor Suzan Roushdy
Professor of Human Genetics
Medical Research Institute
Alexandria

IRAN, ISLAMIC REPUBLIC OF

Dr Dariosh D. Farhud
Professor of Human Genetics
Department of Human Genetics
School of Public Health
Teheran University of Medical Sciences
Teheran

IRAQ

Professor Hanan Hamamy
Professor of Medical Genetics
Faculty of Medicine
Mostansariya University
Baghdad

KUWAIT

Dr Sadika Al-Awadi
Director
Medical Genetics Centre
Maternity Hospital
Kuwait

LEBANON

Dr Ghassan B. Azar
Assistant Clinical Professor
Obstetrics and Gynecology
American University of Beirut
Beirut
OMAN

Dr Anna Rajab
Consultant Paediatrician
Royal Hospital
Muscat

SAUDI ARABIA

Dr Hasan Nasrat
Associate Professor
Department of Obstetrics and Gynecology
King Abdul Aziz University Hospital
Jeddah

Professor Mohsen A. F. Al-Hazmi
Professor, Department of Medical Biochemistry
College of Medicine
King Saud University
Riyadh

UNITED ARAB EMIRATES

Dr L. Al-Ghazali
Department of Pediatrics and Genetics
Faculty of Medicine
Al-Ain University
Al-Ain

Dr Hajer Al-Hosani
Director of Primary Health Care
Ministry of Health
Abu Dhabi

Temporary Advisers

Professor Bernadette Modell
Professor of Community Genetics
Department of Obstetrics & Gynecology
University College
London
UNITED KINGDOM

Dr J. Chapple
Department of Obstetrics & Gynecology
University College
London
UNITED KINGDOM
Professor J. Leonard  
Professor of Paediatric Metabolic Diseases  
Institute of Child Health  
London  
UNITED KINGDOM

Dr V. Der Kaloustian  
Professor and Head  
Division of Medical Genetics  
The Montreal Children’s Hospital  
Montreal  
CANADA

**WHO Secretariat**

Dr M. H. Khayat, Deputy Regional Director, EMRO, Alexandria, Egypt

Dr Ghada Hafez, Director, Health Protection and Promotion, EMRO, Alexandria, Egypt

Dr A. Alwan, Regional Adviser, Non-communicable Diseases, EMRO, Alexandria, Egypt

Dr V. Boutyjenkov, Medical Officer, Non-communicable Diseases, WHO headquarters, Geneva, Switzerland

Mrs Mona El-Herazi, Secretary, EMRO, Alexandria, Egypt