FETAL MEDICINE FOUNDATION (FMF) DEUTSCHLAND e.V.
(Fetal Medicine Foundation Germany, Registered Association)

Version of 24 January 2003

THE „FETAL MEDICINE FOUNDATION DEUTSCHLAND e.V.“

DEFINITION

The Fetal Medicine Foundation (FMF) Germany is a charitable organisation aiming at the establishment, organisation and quality review of a standardised first-trimester examination for pregnant women (11 – 14 weeks of gestation). In the pursuit of its goals, the FMF-Germany principally follows the guidelines established by the FMF UK. However, a number of new suggestions devised in cooperation with the DEGUM have been implemented for use in Germany.

FIRST-TRIMESTER EXAMINATION

The first-trimester screening consists of a focused ultrasound examination of the fetus between the 11th and 14th week of pregnancy. It involves the measurement of so-called “nuchal translucency” and/or the collection of a maternal blood sample in order to determine the biochemical parameters of free beta-hCG and PAPP-A.

In contrast to previous screening methods, which every physician was allowed to perform without specific knowledge, this method is based on a defined standard of performance. This standard is achieved through a certification process which was largely adopted from the parent association FMF-England and adjusted to German conditions

The performance of qualified first-trimester diagnostic testing for fetal malformation allows:

- Early confirmation of an unsuspicious fetal anatomy
- Identification of high-risk groups and focused diagnosis in regard to fetuses with
    - o chromosomal aberrations
    - o cardiac defects
    - o genetic syndromes
    - o skeletal anomalies
- Avoidance of unnecessary invasive interventions in cases with a high likelihood of negative prediction
- Development of early emotional ties with the fetus

Goals

The first-trimester examination is meant to provide all pregnant women with the possibility of undergoing risk evaluation by means of a non-invasive test. However, this requires the implementation of examination standards both in regard to the ultrasound scan and to the biochemical analysis of maternal blood.
This procedure enables every pregnant woman – independently of her age risk, which was hitherto considered alone - to know her individual risk level and to draw her personal conclusions for or against invasive diagnostic testing. To achieve this goal, qualified counselling is of paramount importance.

THE CERTIFICATION PROCESS OF OF THE 11-14 WEEK ULTRASOUND SCAN

The Fetal Medicine Foundation (FMF) UK has established a certification process for the ultrasound examination performed at 11-14 weeks of pregnancy. It aims at ensuring that medical doctors performing this type of ultrasound scan have received adequate training and that the high standard of performance can be reliably maintained by means of ongoing follow-up training and auditing measures. In early 2002, the certification process for Germany was transferred to the FMF-Germany. Laboratory certification, however, continues to be awarded by the FMF UK.

Standardised first-trimester screening includes both the theoretical and practical training of doctors performing ultrasound examinations, and it involves ongoing quality reviews of their work in this field. In addition, a standardised laboratory analysis of the mother's blood sample is carried out. This ensures that the performing laboratories will work in a uniform manner, which in turn guarantees high standards of performance.

Both the certification process and the course material have been adapted to German language use. Participants who have successfully completed both the theoretical examination (multiple choice questionnaire) and the practical examination are certified by the FMF-Germany and then listed as registered sonographers on the websites of both the FMF-Germany and FMF UK.

In order to maintain their certification status, the doctors' recognition of and participation in a continuous quality assurance programme is mandatory. This quality assurance programme provides for the regular submission of specific measurement data and ultrasound images to the FMF-Germany. Particular importance is attached to the fact that certification is restricted to individuals and not transferable to entire departments or practices. The same applies to the distribution of measured values and to the ultrasound images which must be personally obtained as part of the audit. If this requirement is not met, recertification will be denied.

THE CERTIFICATION PROCESS IN DETAIL:

The preliminary requirement for admission to the certification process of the FMF-Germany is a presentation of evidence to the effect that the applicant has sufficient knowledge in the field of prenatal sonography. The minimum requirement to this end is an ultrasound qualification corresponding to DEGUM Level I, or comparable ultrasound education and training. Applicants who are not yet specialists in gynaecology must prove their ultrasound qualification by submitting a DEGUM Level I certificate. FMF Certificates of Competence in nuchal translucency measurement obtained in other European countries are recognised by the FMF-Germany under the above conditions.

The requirements for the certification of medical doctors performing the 11-14 week ultrasound scan are as follows:

- Participation in a theoretical course on the 11-14 week ultrasound scan which must be recognised by the FMF-Germany (**confirmation on participation in the theoretical part**) and successful participation in a multiple-choice question (MCQ) examination (**confirmation on the successful completion of the theoretical examination**).

- Successful completion of a **practical examination**: It comprises the **submission of 5 images showing** that the candidate has the ability to measure nuchal translucency correctly, and it includes a **practical demonstration of an NT measurement**. The 5 submitted images must have been obtained as a result of correct measurement and are

the prerequisite for admission to the practical demonstration. The instructor may issue a **confirmation on the successful completion of the practical examination** only on condition that the 5 images submitted to the instructor/examiner are sufficient evidence of correct NT visualisation and measurement, and provided that practical NT measurement has also been successfully performed.

- The complete set of documents (confirmation on the successful completion of the theoretical and practical examination, DEGUM Level I Certificate) is then sent to the office of the FMF-Germany. After successful certification, the candidate is awarded a Certificate of Competence issued by the FMF-Germany and is registered on the internet page of the FMF-Germany. At the same time, the candidate's name is passed on to the FMF UK.

- The **Certificate of Competence** entitling to the performance of the 11-14 week ultrasound examination can only be obtained **personally**.

- The **practical examination can be repeated** at a later training course run by the FMF-Germany or in the framework of a study visit at an FMF training centre.

- Recertification is required **in 12-month time intervals**. It demands compliance with the requirements of the audit (good distribution of measured values, high-quality ultrasound images as well as correct focusing. Otherwise, recertification may be made contingent upon the applicant’s participation in re-training measures (aiming at a substantial improvement of performance).

THE THEORETICAL COURSE

The FMF-Germany runs theoretical courses, attendance of which leads to the award of a Certificate of Competence entitling to perform first-trimester screening (11-14 wks).

Follow-up ultrasound training can be recognised as a theoretical course in this sense if it is held at one of the recognised training centres of the FMF-Germany. Alternatively, any course in this field can be authorised by the FMF-Germany on condition that this has been so agreed with the officiating president of the FMF-Germany in due time before the course is held, and provided that attendance of a sufficient number of qualified lecturers is ensured.

All medical doctors working in the field of prenatal diagnosis and obstetrics are invited to participate in one of the theoretical courses on the 11-14 week ultrasound scan. The minimum duration of such courses must not be less than **6 hours**. The fee should be as low as possible and should cover the price of the book.

The following list is designed to provide an overview of topics to be covered in the course: Principles of screening examinations, background risk of chromosomal abnormality, risk calculation procedure, invasive diagnostic testing, measurement guidelines for the nuchal translucency scan, diagnosis of fetal malformation in the first trimenon, multiple gestation in the first trimenon, assessment of biochemical parameters, free beta-hCG and PAPP-A. The respective focus may be modified and varied, and should always be consistent with the current state of the art.

The course should involve both a **demonstration of nuchal translucency measurement** and a **live demonstration of risk calculation**. The possibility to complete practical examinations can, but need not be, provided to the course participants.

Principles of the screening examination:

- Data distribution, normal, abnormal, cut-off, false-positive rate, false-negative rate, probability quotient (abnormal/normal), principles of risk modification through multiplication by probability quotient

Screening based on maternal age:

- Maternal age distribution, age of 35 (rising risk with increasing age)
- Background risk of trisomies 21, 18 and 13
- Background risk of sex chromosome disorders, Turner syndrome, triploidy
- Background risk and gestational age (decreasing risk with rising number of weeks)
- Risk in the case of previous histories of trisomy 21, 18, 13 (background +0.75%)
- Risk in the case of previous histories of sex chromosome disorder, Turner syndrome, triploidy (background +0%)

Measurement guidelines for the nuchal translucency scan:

- **11+0** until **13+6 weeks of gestation**
- **45-84**mm **crown-rump length**
- Mid-sagittal section, neck position parallel to transducer head
- Image magnification (the fetus should occupy at least 75 % of the image, maximum interval spacing of measurement 0.1 mm)
- Neutral position (flexed, hyper-extended, umbilical cord)
- Largest distance between the two lines, in right angle (90°)
- Placement of callipers on the lines, in as close a position as possible to translucency

Percentile curves

- Crown-rump length
- Nuchal translucency

Nuchal translucency studies:

- Snijders Study (n = 100 311, T21 = 326)
  (T21 NT ≥ 95th percentile 72%, normal 5%, T21 risk ≥ 1:300 82%, normal 8.3%)
- Zoppi Study (n = 12 499, T21 = 64)
  (T21 NT ≥ 95th percentile 80%, normal 5%)
- The German-language study (n = 23 805, T21 = 210)
  (T21 NT ≥ 95th percentile 83%, normal 8%, T21 risk ≥ 1:300 87, 6%, normal 13%)
- Meta-analysis (n = 86 012, DR = 79%, FPR = 3%)

First-trimester serum biochemistry: Which serum picture matches which chromosomal disorder

- Free beta-hCG: increased in trisomy 21
- PAPP-A: decreased in trisomy 21
- Trisomies 18 and 13, Turner syndrome, triploidy (both forms)
- OSCAR principles (one-stop clinic for assessment of risks)
  - o patient information: 85-90% sensitivity, 5% false positive
  - o nuchal translucency measurement, serum analysis
  - o result disclosure: demonstration of findings (FMF software)
  - o decision-making
  - o possible invasive testing
  - o follow-ups as an integral part of quality assessment

Ductus venosus:

- Matias study: reverse flow, normal: 3.1% (13/423), chromosomally abnormal: 57/63 (91%)

Nasal bone:

- Cicero study: NB (-): T21 73% (43/59, LR 146), normal 0.5% (3/603, LR 0.27%)

Statistical models on various combinations of non-invasive diagnostic testing:

- Age, NT, NB, biochemistry, ductus venosus
- NT followed by second-trimester serum biochemistry
- NT followed by second-trimester ultrasound

Invasive diagnostic testing:
Indications, point of time, rates of miscarriage, leakage, method, mosaics (CPM)

- Chorionic villus sampling (from 11+0 weeks of gestation onward): direct preparation, long-term cultivation
- Amniocentesis (from 16+0 weeks of gestation onward): FISH
- Amniocentesis (from 14+0 weeks of gestation onward)
- Cordocentesis (from 20+0 weeks of gestation onward); Rh incompatibility, alloimmune thrombocytopenia, parvovirus B19
- Studies: Nicolaides, Sundberg, Tabor, Canadian

Malformations in the first trimenon:

- Increased NT and normal karyotype
  - genetic syndrome: Souka studies
  - skeletal anomalies: extracellular matrix (genetic table)
  - cardiac defects: Hyett studies
- CNS anomalies: acrania/exencephaly/anencephaly, encephalocele, Meckel-Gruber syndrome, hydrocephalus/hydranencephaly, Dandy-Walker malformation, holoprosencephaly, iniencephaly, spina bifida
- Abdominal wall defects, omphalocele, gastroschisis
- Urogenital malformations: renal aganesis (bilateral), infantile polycystic renal disease, multicystic dysplastic renal disease, hydronephrosis, megacystis
- Skeletal anomalies: caudal regression syndrome

Multiple gestations:

- Zygosity, chorionicity, amniocity
- Miscarriages, premature deliveries, perinatal mortality, IUGR
- TTTS: diagnostic criteria, conservative/surgical treatment
- Death / Structural anomalies of the fetus and pertinent management
- Chromosomal disorders: choice of invasive diagnostic method (AC versus CVS)
- Reduction of multiple pregnancies and embryo reduction.

The content of the course is also dealt with in the book “The 11 - 14 Week Scan: The Diagnosis of Fetal Abnormalities”, KH Nicolaides, NJ Sebire, RJS Snijders, Parthenon.

THE THEORETICAL EXAMINATION

The theoretical part of the course ends with a multiple-choice question examination. It aims at ensuring that candidates have fully understood the course content. The course is considered

completed successfully if **70% of the questions** have been answered correctly. If the candidate has passed the theoretical examination, he or she will receive a confirmation to this effect.

THE PRACTICAL EXAMINATION

The practical examination consists of two parts: a. the submission of **5 high-quality ultrasound images** evidencing correct NT measurement and b. the **practical demonstration of an NT measurement**. This examination aims at ensuring that nuchal translucency is measured in compliance with the FMF guidelines.

A. SUBMISSION AND EVALUATION OF 5 ULTRASOUND IMAGES OBTAINED THROUGH NT MEASUREMENT

Prior to the practical demonstration, 5 ultrasound images evidencing correct NT measurement of 5 different fetuses must be submitted to the authorised course instructor / examiner.

The candidate is required to enclose a **written confirmation** along with image submission in which he or she certifies to have performed and documented the 5 measurements personally.

Requirements on ultrasound images:

- The image should provide a good mid-sagittal view of the fetus,
- The fetal image must be sufficiently magnified (the fetus should occupy at least 75% of the image),
- Fetal skin surface should be visible separately from the amnion,
- Head position should be neutral,
- Calipers should be correctly positioned at the point of maximum translucency thickness

Image evaluation:

Image No.	Section plane **(0-2)**	Magnification **(0-2)**	Amnion **(0-2)**	Head position **(0-2)**	Caliper positioning **(0-2)**	Score
1						
2						
3						
4						
5						

Scores (0, 1, 2)

Section plane	(rotated: 0, slightly rotated 1, mid-sagittal: 2),
Image magnification	(insufficient: 0; near correct: 1, >75% or detail 2),
Amnion	(not visible: 0; visible: 1, skin and amnion: 2),
Head position	(too strongly flexed, hyper-extended: 0; near correct: 1, neutral: 2),
Caliper positioning	(wrong positioning: 0; near correct: 1, correct: 2).

Score system:

(I)	very good	(9-10)
(II)	good	(7-8)
(III)	insufficient	(0-6)

Renewed submission of images: If the score attained on one or several images falls short of 7 points, a corresponding number of newly obtained images must be submitted. Only when all 5 images have been recognised can the candidate be admitted to the practical NT demonstration.

B. PRACTICAL DEMONSTRATION OF NT MEASUREMENT

- Candidates must demonstrate in at least one case that they are capable of correctly visualising and measuring nuchal translucency. To this end, a photo must be produced which complies with the specified minimum requirements and which will be evaluated according to the above-listed score.

  The practical demonstration part of the examination is considered completed successfully if a minimum score of 7 out of 10 points has been achieved in image evaluation.

- Furthermore, candidates must provide practical evidence in one case that they know how to use the FMF software in order to provide the patient with an explanation of diagnostic results displayed on the screen. Elucidation must be provided in such a manner that the patient is in a position to understand the significance of risk figures and to which degree the background risk has changed after performance of nuchal translucency measurement and, if applicable, after completion of biochemical analysis.

- Candidates should moreover exhibit their knowledge of possible follow-up measures. They should be in a position to offer performance of such measures themselves or in cooperation with an appropriate specialist centre.

TRAINING CENTRES OF THE FMF-GERMANY

Candidates whose standard of performance requires improvement shall be given the opportunity to contact one of the FMF training centres listed in the Appendix to this Charter. These centres also offer the possibility to complete a practical examination in nuchal translucency measurement.

The recognition as an FMF training centre is awarded by the FMF-Germany, as required, following an application to the officiating President.

FMF TRAINING INSTRUCTORS

Persons wishing to act as FMF training instructors must meet the following requirements:

1. Specialist status in gynaecology and obstetrics
2. Seminar instructor DEGUM Level II (prenatal focus)
3. Mastery of invasive diagnostic procedures
4. Valid FMF Certificate of Competence
5. Organisation of advanced training in prenatal diagnosis within a period of 2 years
6. The training instructor must be available for practical examinations

CERTIFICATE OF COMPETENCE

Upon submission of the confirmation that both the theoretical and practical examination entitling to perform the 11-14 week ultrasound scan have been successfully completed, issuance of the Certificate of Competence can be applied for at the office of the FMF-Germany. The award of the Certificate allows the receipt and use of the FMF risk assessment software. The Certificate is awarded personally and is not transferable.

Medical doctors who have not yet obtained certification, but work at a facility in which at least one doctor is certified, are also allowed to perform nuchal translucency measurements. However, the measurement data obtained by them must be reviewed by the certified examiner until these doctors have themselves obtained certification.

Following the award of the Certificate of Competence, the awardee's name, postal address and e-mail address are registered on the website of the FMF-Germany. The awardee receives a Certificate with a registration number entitling him to receive a single-user version of the first-trimester software from a software company also certified by the FMF-Germany.

The **Certificate of the FMF-Germany** carries the FMF seal, embossed with the year of issue, and a DEGUM plate.

SOFTWARE

Once the certification holder has received the FMF registration number, he or she can contact an FMF-certified software company for first-trimester risk calculation. The respective company will then supply a free single-user version of the first-trimester risk calculation software. Alternatively, a full version of the Fetal Database for the first and second trimenon which offers a wider range of investigation options can be purchased from these companies.

Risk calculation always requires the submission of the Certificate of Competence in nuchal translucency measurement and communication of the certification number.

The single-user version of the first-trimester risk calculation software must comply with a variety of requirements. It must offer the following features:

- Relicenseability (supply of a Risk Dat or a certification string)
- Access to the database of the previous year after recertification
- Upgradability to the full version of the Fetal Database without loss of data
- Auditability (cf. Appendix)
- Suitability for medical reports
- German language user interface

THE AUDIT: THE ONGOING ANNUAL QUALITY REVIEW

The FMF software must be renewed in time intervals of 12 months. This can either be done through an update, or by means of a certification string or file. Renewal is granted when the FMF-Germany, after reviewing the distribution of measured values and the quality of ultrasound images, considers the results to be satisfactory.

Holders of the Certificate of Competence in nuchal translucency measurement will receive an e-mail some time prior to the expiry of their software, requesting them to send an **audit file along with five ultrasound images** to the FMF Audit Centre (for the address, please see the website of the FMF-Germany: **http://www.fmf-deutschland.info**). When these have been received, several assessments will be performed on the audit data set, with the primary focus being on the statistical description of data and on the quality review of ultrasound images.
If the audit brings to light considerable deviations, the applicant will be required to attend additional training courses qualifying him for recertification.

Recertification is awarded personally and is not transferable.

When a certified physician has successfully undergone his or her re-audit and is thus eligible for recertification, the Audit Centre will inform the respective software companies accordingly. The latter will then send the required software or certification strings to the certified physician, who will in turn be able to gain access to his or her software for a further twelve-month period. The FMF-Germany will inform the FMF UK as to which physicians have obtained recertification, so that both the internet pages of the FMF-Germany and those of the FMF-UK can be kept up to date.

If a physician has obtained the Certificate of Competence in nuchal translucency measurement, but prefers risk calculation to be performed by an **FMF-certified laboratory**, the FMF-certified laboratory conducting the assessment is **responsible** and **under the obligation** to provide the respective physician **once a year** with all the **data required for his audit** so that the physician can pass the data on to FMF-Germany in order to be re-licensed.

The award of certification places the certification holder under the obligation to participate in the quality assurance measures demanded by the FMF-Germany and to use his or her best efforts to provide the FMF with follow-up data on an ongoing basis.

FEES

A. FEES CHARGED FOR THE ISSUANCE OF A CERTIFICATE OF COMPETENCE

Colleagues who have successfully completed both the theoretical and the practical examination and who have informed the FMF-Germany accordingly, will receive a Certificate of Competence with a DEGUM seal from the FMF-Germany. The applicant has to pay a **handling fee of € 50**.

If the theoretical and/or the practical examination has/have been completed abroad, certification may be granted against payment of a **handling fee in the amount of € 80**. The price is inclusive of the Certificate of Competence, however, it does not include the NT book.

B. FEES CHARGED FOR RECERTIFICATION

A **fee of € 80** per applicant is charged for the required annual recertification.

C. LICENCE FEE FOR COURSE ORGANISERS

If an organiser implements an **advanced FMF training course** leading to a theoretical examination, a **licence fee of € 40** per course participant must be paid to the FMF-Germany. The accompanying course book can be purchased from the FMF-Germany at a **special price** of **€ 40**.

THE CERTIFICATION PROCESS FOR LABORATORIES

Laboratories are also eligible for certification via the FMF-Germany. All the pertinent details can be gleaned from the **Declaration of Conformity** for Laboratories. Its essential requirements reside in the laboratories' confinement to the use of FMF-certified analytical systems, their participation in interlaboratory trials (UKNEQAS), and their disclosure of risk assessment to only those sonographers who have obtained certification from the FMF-Germany, whereby this risk assessment may be based **solely** on first-trimester biochemical screening or on both first-trimester screening **and** nuchal translucency measurement.

A responsible member of the laboratory must have attended a theoretical course.

FEES

First-time certification:		**€ 1,500.00**
Recertification:	**for the first 1,000 examinations:**	**€ 0.75 per examination**
	above 1,000 examinations:	**€ 0.50 per examination**

The fees due to the FMF-Germany are levied for the implementation of quality assurance **[Declaration of Conformity: see Appendix].**

PROCEDURAL RECOMMENDATIONS FOR FIRST-TRIMESTER SCREENING (11-14 WEEKS OF GESTATION)

PRE-EXAMINATION COUNSELLING (11-14 WEEK ULTRASOUND SCAN)

The patient's participation in first-trimester screening is voluntary.

Experiences gained from recognised Pregnancy Conflict Counselling Centres in Germany show that many pregnant women are not sufficiently informed about the possibilities and limits of prenatal diagnosis and about consequences to be drawn from suspicious findings. Therefore, it must be ensured prior to examination that the respective woman has had sufficient time to obtain information as to which consequences may result from an examination: Diagnosis of fetal malformation in approx. 3-5 % of all cases, reduction of the trisomy 21 risk in approx. 90-95 % of cases, unchanged or increased risk of trisomy 21 in approx. 5-10 %, chorionic villus sampling in approx. 5 %, miscarriage following invasive intervention in approx. 1 %, diagnosis of trisomy 21, delivery of a child affected by trisomy 21, induced abortion. Pertinent information leaflets which may be obtained from the website of the FMF-Germany (http://www.fmf-deutschland.info) or from other counselling centres will be helpful in this respect. A physician's interview conducted prior to the examination will contribute to remedying a possible lack of medical information and will solve problems of understanding.

In the framework of normal prenatal care, women and parents shall have the right to decide freely, after being fully informed, as to which prenatal examinations they would like to have performed in their case. Pertinent methods of prenatal care should therefore be dispensed with as long as the respective parties have not been informed. The right of women and parents to choose not to be informed as to whether their child may be born with a handicap must be respected at all times.

POST-EXAMINATION COUNSELLING (11-14 WEEK ULTRASOUND SCAN)

The main advantage of first-trimester malformation screening including nuchal translucency measurement is that it offers the **possibility to calculate** and **disclose** the risk of trisomies 21, 18 and 13 **right after the examination**. To do so, the free-of-charge version of the programme for first-trimester risk assessment can be used, whereby the risks can be visualised graphically on a screen for further explanation.

If the ultrasound scan yields a **suspicious nuchal translucency value** (NT>95th percentile), a **suspicious risk assessment** (>1:300) for trisomy or a malformation, the respective woman should be counselled to have a follow-up examination performed at a medical centre focusing on prenatal diagnosis. There she may obtain genetic counselling and undergo invasive diagnostic testing. If the diagnosis of chromosomal abnormality is established, parents can be informed about the type of disorder and its prognosis as well as about options for therapy. If the parents wish to terminate the pregnancy, and if there is an indication for induced abortion, it is recommended that the woman and the couple, respectively, be carefully prepared for the termination of pregnancy and the ensuing period of mourning by having ready access to psychological care which also protects them from taking precipitous decisions in a state of shock.

Once a diagnosis of first-trimester malformation has been established, post-examination counselling must take into account that a sufficiently reliable ultrasound diagnosis of a number of malformations or disorders, irrespectively of whether nuchal translucency values have been

rated as suspicious or not, will only be possible at a later stage of pregnancy (18-23 weeks) and that some malformations may even remain undetected.

COUNSELLING AFTER ULTRASOUND EXAMINATION AND BIOCHEMICAL ANALYSIS (11-14 WEEKS OF GESTATION)

If the examination includes first-trimester biochemical analysis of the mother's serum (free beta-hCG and PAPP-A), there are basically several counselling options.

Relatively few centres will offer the possibility to perform an analysis of the mother's blood sample in conjunction with the ultrasound scan (One-Stop Clinic for Assessment of Risks (OSCAR)), so that the patient can be informed about the initial risk and the overall risk (based on maternal age, NT and biochemical result) right at the end of the examination.

As a rule, however, a maternal blood sample will be collected, with the result of the analysis being available one or two days later.

Taking all this into account, patient information may take different forms:

- The result of nuchal translucency measurement is disclosed right at the end of the ultrasound examination. When the results of the biochemical analysis are available, the overall risk is calculated anew, and the physician who has performed the examination will announce the result to the patient over the telephone.
- If the measured value is below the 95th percentile, no risk information will be provided to the patient right after nuchal translucency measurement. Only when the risk factor has been assessed conclusively following the analysis of all results (NT and biochemical analysis of maternal serum) will the physician who has performed the ultrasound scan announce his findings by telephone some days later.

In approximately 85 - 90 % of all cases, both nuchal translucency measurement and the biochemical analysis will lead to a **reduction of the risk**. In some 10 - 15 % of cases, however, nuchal translucency measurement will **reduce the risk**, whereas maternal serum analysis will **increase the risk**. Even in cases where the overall risk (NT and biochemical analysis of maternal serum) has diminished in comparison with the initial risk, considerable uncertainty may ensue on the mother's side, which may be remedied solely by invasive diagnostic testing.

In order to avoid both this counselling dilemma and unnecessary invasive intervention, blood analysis can be performed some days prior to the ultrasound scan so that the biochemical result will be already available on the day of ultrasound examination. This, too, will allow a comprehensive assessment of the overall risk at the end of the ultrasound examination.

DEVICE PREREQUISITES FOR NT MEASUREMENT AND PERFORMANCE OF FIRST-TRIMESTER EXAMINATION (ULTRASOUND EXAMINATION AND MATERNAL SERUM BIOCHEMISTRY)

DEVICE PREREQUISITES FOR NT MEASUREMENT

In order to perform nuchal translucency measurement correctly, particular attention must be paid to the ultrasound device used because it must comply with a number of minimum technical requirements:

- 5-MHz-probe or adequate broad-band probe
- Cine loop
- Zoom
- Precise calipers (if possible cross-shaped calipers)
- Caliper increment 0.1 mm.

PERFORMANCE OF THE FIRST-TRIMESTER EXAMINATION

Ideally, the results of both nuchal translucency measurement and biochemical analysis of maternal serum are obtained on the same day. The gynaecologist who has performed the ultrasound examination will then inform the patient about her initial risk and her residual risk (based on age, NT and maternal biochemistry).

Occasionally, a sonographic marker (soft marker) is diagnosed as an indication of chromosomal disorder between weeks 18 and 23 of gestation. It has now been possible to determine the probability quotients of the various markers indicating an increased risk for trisomy 21, 18 or 13 quite reliably, however, the **prognostic significance of these markers considerably depends** on whether nuchal translucency measurement is performed, or rather a serumbiochemistry of the first or second trimester; and it also depends on the **quality** of these investigations.

It is therefore **indispensable** for the interpretation of these sonographic markers that

- a **thermoprint of nuchal translucency measurement** is **enclosed** in the mother’s passport
- a **printout of the risk calculation** (NT, biochemical analysis) is **enclosed** in the mother's passport

for every nuchal translucency measurement.

The result report must also indicate whether the sonographer and/or the laboratory hold(s) a Certificate of Competence issued by the FMF-Germany.

In the event of a suspicious NE result (NT > 95th percentile), the patient should be referred to a centre for prenatal medicine (DEGUM Level II/III) in order to undergo further diagnostic testing. The tasks of such higher-level centres consist in establishing targeted malformation diagnoses as well as in informing patients about the further management, and – if required – in implementing invasive diagnostic testing (chorionic villus sampling).

If no further sonographically suspicious result is found despite increased nuchal translucency values, the patient should be recommended to to undergo a further targeted ultrasound examination between weeks 18 and 22 of gestation.

APPENDIX

DECLARATION OF CONFORMITY

PRENATAL INVESTIGATION IN THE FIRST TRIMESTER

RECOMMENDATIONS AND COMPLIANCE FOR LABORATORY GLP

D e c l a r a t i o n o f C o n f o r m i t y

We, the laboratory

full name of the lab: ……..
complete address: ……..
……..
Telephone No: ……..
Fax No: ……..
e-mail address: ……..
Responsible contact person: ……..

declare the following in order to achieve the certification by the FMF, London:

1. We are CPA (UK) Ltd accredited or accredited by an equivalent country standard.

2. We intend to have a workload exceeding 1000 screens per year at the end of 2003 at the latest.

3. We participate in the UKNEQAS scheme for 1st Trimester Down's Syndrome Screening. Our participant No. is ....

4. We will demonstrate that our performance in the UKNEQAS scheme is acceptable i.e. that our analytical Bias from the Method Mean for Free Beta hCG and PAPP-A does not deviate by more than +/- 10% on an ongoing basis.

5. We perform all Prenatal Risk Calculations only using Fetal Medicine Foundation approved software which uses the Fetal Medicine Foundation risk algorithm.

6. We ensure that we take nuchal translucency measurements after March 31, 2003 only from Fetal Medicine Foundation accredited Sonographers or Obstetricians/Gynaecologists.

Up to this date we will also accept nuchal translucency measurements from colleagues that have already participated in a training programme for NT measurement.

7. We ensure that if we receive samples as whole blood that they are received within 48 hours of collection. If samples are received as serum this must be within 72 hours of collection. Use of material outside of these limitations could result in invalid Free Beta hCG results being produced.

8. We only analyse samples when the referring centre has provided a minimum data set with the request. Samples will only be analysed when the gestation is between the limits 11 week 0 days to 13 weeks 6 days.

   The minimum data set includes:

   Forename & Surname
   Gynaecologist & Referral centre address
   Patient Date of Birth
   Previous history of T21/T18/T13
   Maternal weight
   Date of NT & CRL
   NT measurement
   CRL Measurement
   Multiple Pregnancy Status
   Date of Blood Sample
   Specimen reference number

   Optional items are Smoking status and ethnic origin

9. We ensure that we use the KRYPTOR® instrument and KRYPTOR® reagents for Free Beta hCG and PAPP-A or any other instruments and reagents for the same markers provided that such instruments and reagents are approved by the FMF UK for the purpose of prenatal screening in the 1st trimester. Such assay systems must have demonstrable proven clinical performance for this use.

10. We perform Internal Quality Control procedures with each batch of samples analysed – or on a daily basis. Three level QC will be performed for the analytes Free Beta hCG and PAPP-A.

11. We commit on demonstrating the following between day CVs.

	Free Beta - hCG		PAPP-A	
	Conc	CV	Conc	CV
Level 1	85	3.0	0.30	4.0
Level 2	20	3.0	1.50	4.0
Level 3	8	3.5	4.0	3.5

12. We will also give consideration to monitoring the variability of the risk derived from a fixed maternal age, fixed gestational age and fixed NT using results from the Level 1 control. At a target risk of 1 in 250 a 10% CV of the risk should be achievable.

13. We will take part in the annual Fetal Medicine Foundation audit of laboratories.

14. We will make best efforts to follow up the outcome of all pregnancies screened or at least those identified with a risk of 1 in 300 or greater.

15. We will monitor the overall median MoM for Free Beta hCG and PAPP-A on a monthly basis. This should be within the limits 1.00 +/- 10%.

16. We will monitor the individual completed weekly medians on a 3 monthly basis to ensure they do not deviate from the expected values by more than +/- 10%.

17. The percentage of total screened cases identified with a risk of 1 in 300 or greater will be monitored on a monthly basis. Depending upon the age of the population being screened this should not be greater than 6% and less than 3%.

……
Laboratory (stamp)

…… ……
Location / Date Signature

TRAINING CENTRES OF THE FMF-GERMANY:

The current list comprises:

Berlin:	Prof. Dr. R. Chaoui, Charité (DEGUM III) Praxis Drs. Albig, Prof. Dr. Becker, Entezami & Gasiorek-Wiens
Bonn:	Prof. Dr. U. Gembruch, Uni-Klinik (DEGUM III)
Dresden:	Dr. G. Kamin, Uni-Klinik Dr. W. Seefried
Dusseldorf:	Dr. B. Tutschek, Uni-Klinik (Diploma in Fetal Medicine) Praxis PD. Dr. P. Kozlowski (DEGUM III)
Frankfurt/M.:	Prof. Dr. E. Merz, (DEGUM III) Praxis Dr. M. Bielicki
Freiburg:	Praxis Dr. M Schulte-Vallentin
Hamburg:	Prof. Dr. H-J. Hackelöer, AK Barmbek (DEGUM III)
Hannover:	Dr. R. Schwerdtfeger
Hildesheim:	Prof. Dr. R. Osmers (DEGUM III ass.)
Kiel:	Dr. C. v. Kaisenberg, Uni-Klinik (Diploma in Fetal Medicine)
Leipzig:	Prof. R. Faber, Uni-Klinik
Ludwigsburg:	Praxis Dr. H. Meyberg
Mainz:	Dr. F. Bahlmann, Uni-Klinik
Munich:	Prof. KTM Schneider, Rechts der Isar, TU (DEGUM III ass.) Praxis PD. Dr. T. Schramm (DEGUM III)
Nuremberg:	Praxis Dr. A. Kossakiewicz
Peine:	Praxis Dr. M. Pruggmayer
Schwäbisch Hall:	Prof. Dr. A. Rempen (DEGUM III)
Willich:	Dr. B. Berschick

TRAINING CENTRES OF THE FMF-AUSTRIA:

Graz:	Prof. Dr. M. Häusler, Uni-Klinik (DEGUM III)
Innsbruck:	Prof. Dr. P. Schwärzler, Uni-Klinik Prof. Dr. C. Brezinka, Uni-Klinik
Linz:	Dr. W. Arzt, Landesfrauenklinik
Salzburg:	Prof. Dr. A. Staudach, Landesfrauenklinik (DEGUM III) PD Dr. H. Steiner, Landesfrauenklinik (DEGUM III)
Vienna:	Prof. Dr. G. Bernaschek, Uni-Klinik (DEGUM III) Prof. Dr. J. Deutinger, Uni-Klinik (DEGUM III) PD Dr. Krampl, Uni-Klinik PD Dr. E Hafner, Donauspital Dr. K. Schuchter, Donauspital