αlpha™

Antenatal screening software for Down's syndrome, open neural tube defects, and pre-eclampsia

For use in first trimester, second trimester and Integrated screening for Down's syndrome and pre-eclampsia and second trimester screening for open neural tube defects

Version 8

User manual

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Manual Issue 2

WELCOME TO αlpha 8

We, at Logical Medical Systems Limited, seek to produce the best possible screening software. Our priority is to make screening as effective and safe as possible, introducing regular improvements to the software, so that scientific advances in screening are available as soon as possible. We also aim to provide the means to regularly monitor a screening service so that users are able to check the performance and quality of their screening programmes. We hope that you find this manual helpful. We would welcome any comments and suggestions on how it might be improved. Please email us with your comments to **alpha@lmsalpha.co.uk**. This manual is for use with **αlpha** version 8.0.14136.23 and later.

WARNING:

All intellectual property rights subsisting in **αlpha** are vested in Logical Medical Systems Limited, and the user shall have no rights to use, copy, modify or merge the software, save as is permitted by the user's licence agreement with Logical Medical Systems Limited.

The user should note that there may be intellectual property rights owned by third parties which could be affected by the use of **αlpha**. Logical Medical Systems Limited gives no warranty or indemnity that use of **αlpha** will not infringe any third party's intellectual property rights. The user is responsible for ensuring that it has any third party rights necessary to use **αlpha**.

Logical Medical Systems Limited is not responsible for clinical decisions or actions that are taken in conjunction with the use of **αlpha**. All interpretations produced by **αlpha** should be assessed by an experienced physician in conjunction with the other factors judged relevant by that physician.

Screening for Down's syndrome, open neural tube defects and pre-eclampsia does not detect all affected pregnancies, and some women with unaffected pregnancies will be classified screen-positive. Not all pregnancies affected with trisomy 18 (Edward's syndrome), trisomy 13 or Smith-Lemli-Opitz syndrome can be identified, and some women with unaffected pregnancies will be classified as being at increased risk of having a pregnancy with one or both of these disorders.

Should the user's computer fail, or be shut down incorrectly, while **αlpha** is in use, data entered but not saved should be regarded as suspect and re-entered.

αlpha should only be used by operators who have received training in its use.

IMPORTANT: Regular backup of αlpha data is essential. Backups should be made weekly as a minimum, and preferably after each day's use of αlpha. The use of regularly updated anti-virus software is recommended. Failure to follow these recommendations could lead to the irretrievable loss of data, for which Logical Medical Systems accepts no responsibility.

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1 Introduction

1.1 About αlpha version 8

Welcome to **αlpha**, the leading interpretive software for use in antenatal screening for Down's syndrome, open neural tube defects (NTDs) and pre-eclampsia. **αlpha** was the first software of its kind, originally developed in 1987 by Professor Wald and Professor Cuckle, and it is still the standard against which most others are compared. It is based on published scientific data on antenatal screening and diagnosis, and is regularly updated in the light of new scientific advances *(*see Section 7: References*)*. **αlpha** has been used in screening over 9 million women in 49 countries.

αlpha uses a woman's age, the concentration of serum markers for Down's syndrome and NTDs, and other information about the pregnancy, to estimate the woman's risk of having a pregnancy with either of the two disorders. [1, 7] The ultrasound markers nuchal translucency [28] and ductus venosus pulsatility index[81], the presence or absence of fetal nasal bone [52] and the use of ductus venosus blood flow as a categorical marker [86] can also be used in estimating the risk of Down's syndrome, if desired. **αlpha** also uses the concentration of first trimester mean arterial pressure and the first and second trimester serum markers to estimate the risk of the pregnancy developing pre-eclampsia [80,8993,94]. You can choose to print the risk of trisomy 18 (Edward's syndrome) [18,19,36], trisomy 13 [82,83,84] or Smith-Lemli-Opitz syndrome (SLOS) [34,47], if they are high. **αlpha** is suitable for first trimester, second trimester and integrated screening for Down's syndrome.

It also interprets amniotic fluid (AF) alpha-fetoprotein and acetyl cholinesterase (AChE) results used in the diagnosis of open neural tube defects.[8]

αlpha version 8 is a major step forward, incorporating the latest medical and scientific advances in antenatal screening for Down's syndrome from the scientific literature including SURUSS, the Serum, URine and Ultrasound Screening Study.[49,51,58,88] SURUSS is the report of a large collaborative study designed to identify the safest and most effective method of antenatal screening for Down's syndrome, using nuchal translucency, and first and second trimester biochemical markers, together with maternal age, in various combinations.

αlpha is licensed to interpret the Integrated Test.38 The Integrated Test providies safer and more effective Down's syndrome screening than ever before.

There are also technical improvements that make **αlpha** more flexible and easier to use than ever before. No other software of its kind offers such a wide range of facilities or quality control features.

1.2 Getting started

Your **αlpha** software will be installed by an approved installer, who will:

- help you set up the software according to your needs
- provide training in the use of **αlpha**

Only operators who have received training in the use of **αlpha** from an approved installer should use **αlpha**. He or she will assist you in setting up **αlpha** for you to use. You will find more information on the steps involved in setting up **αlpha** in the following sections of this manual:

- Section 2 General Principles
- Section 3 Set-up

1.3 Data entry and reporting

As well as entering data manually using a form, which you can design yourself, data can be imported from files generated by other software. Assay results can be transferred automatically from your laboratory equipment to **αlpha**. You can export screening data from **αlpha** to other systems and to your spreadsheet or database software.

The manual and automatic methods of data entry are fully interchangeable, and they can be combined in a way that suits the way you work. For example, you could import part of a patient's record from a laboratory information management system (LIMS), then manually enter other data, such as ultrasound information, which may not be available on the LIMS, and then merge this automatically with test results from your analyser.

For more information on the different methods of data entry available in **αlpha**, refer to:

- *Section 4.1* Data Entry
- *Section 4.5* Import

Our philosophy is that patient reports should be simple, informative and clear, and **αlpha**'s reports achieve this. Reports are stored in a database, allowing you to reprint a copy of any report. If changes or additions are made to a report, **αlpha** retains both the original report and all modified versions, so a full report history is available for every woman screened.

For more information on creating and modifying reports in **αlpha**, refer to the following sections of this manual:

- *Section 4.2* Reporting
- *Section 4.3* Searching
- *Section 4.4* Edit reports

1.4 Test interpretation and risk estimation

The method which **αlpha** uses to estimate the risk of a woman having a Down's syndrome pregnancy is based on determining the age-specific risk of Down's syndrome [46,55], and modifying it in the light of the screening marker levels, using a multivariate log-Gaussian model derived from published parameters [49].

The log-Gaussian model [7] is used to generate a likelihood ratio (LR), which is used to modify the age-specific risk, according to the levels of the different screening markers, as follows:

Test specific risk (as an odds ratio) = Age specific risk (as an odds ratio) x LR

The marker levels are expressed as multiples of the median (MoM) in unaffected pregnancies of the same gestational age, thereby allowing for changes in the normal median with gestational age, and for systematic differences between laboratories and between assay reagents.

The MoM values may be adjusted to allow for other factors that affect the normal median value, such as maternal weight [13,26], ethnic group [23], insulin-dependent diabetes mellitus [14], multiple pregnancy [10,11,48,57], *in-vitro* fertilization [39], and smoking [45,69,97].

By using MoM values in this way, **αlpha** is independent of the assay reagents used. **αlpha** provides a wide range of statistical facilities that enable you to monitor the normal medians, and to change them if necessary; for example, to correct for drift in the normal medians, or if you decide to change the assay reagents used.

αlpha can also identify cases where a single marker has a very large influence on the risk estimate[65]. In these cases, **αlpha** will notify the user of the anomalous marker and give them the opportunity of removing it from the risk estimate in the screening report.

Women who have had a false-positive screening result in one pregnancy are much more likely to have a one in a subsequent pregnancy than women in general.[50, 59] **αlpha** can help to avoid this by adjusting serum marker levels in women who have been screened in a previous pregnancy and who have not had a previous pregnancy with Down's syndrome.

The methodology underlying risk estimation has been validated empirically. Studies have found that the risk of Down's syndrome predicted by **αlpha** is in close agreement with the observed risk.[29,33,67]

The method **αlpha** uses to estimate the risk of a woman developing pre-eclampsia is based on modifying the pre-eclampsia prevalence in light of the screening marker levels together with the history of a previous pregnancy with pre-eclampsia, using a multivariate log-Gaussian model derived from published parameters [80,89,93,94].

1.5 Monitoring screening performance

αlpha provides a range of valuable monitoring features to help you achieve the best screening performance.

For example, with **αlpha** you can:

- examine and correct drift in the normal median values of the screening markers
- obtain estimates of the expected screening performance given the age distribution of your population; you can then compare this with the screening performance observed in practice.
- obtain an estimate of the expected number of Down's syndrome term births in the screened population, in the absence of screening and therapeutic abortion; this can be compared with the total number of Down's syndrome pregnancies identified.

For further information on monitoring your screening programme, refer to:

- Section 5.2 Analyse-it
- Section 5.10 Report summary
- Section 5.4 Median Analysis
- Section 6 Monitoring your Screening Program

1.6 Choice of screening markers

αlpha version 8 contains the statistical parameters (means, standard deviations and correlation coefficients) used in screening with the serum markers alpha-fetoprotein (AFP), unconjugated oestriol (uE_3), total and free ß human chorionic gonadotrophin (hCG) and inhibin-A in second trimester screening (between 14 and 22 weeks of pregnancy), and with total and free ß hCG, pregnancy associated plasma protein A (PAPP-A), placental growth factor (PlGF), nuchal translucency (NT) and ductus venosus pulsatility index[81] (DVPI) in first trimester screening (between 10 and 13 weeks of pregnancy).

First and second trimester screening markers may be used in combination to provide a single estimate of risk, in the Integrated Test.[38] *(see Section 1.8 The Integrated Test)*

Sequential testing[64] can also be performed in which early completion of screening is allowed for women with very high risk pregnancies identified in the first trimester. Nearly all women proceed to the full Integrated test. (See section 4.2.5 Sequential testing*)*

αlpha version 8 can interpret the ultrasound finding of present or absent fetal nasal bone[52] and use ductus venosus blood flow as a categorical marker[86] in estimating the risk of having a pregnancy affected with Down's syndrome.

N.B. There are intellectual property rights covering the use of some screening markers and screening tests (e.g. the Integrated Test), and users need to ensure that they have the legal right to use them.

1.7 Multi-user version

αlpha is available in a basic single-user configuration, or with multi-user access. With multi-user access, more than one user can access the **αlpha** database simultaneously from different workstations on a local area network (LAN).

Benefits of multi-user access include:

- increased throughput - several users can enter data simultaneously at different workstations
- greater convenience - reports can be viewed or printed from any location on the network

αlpha is compatible with most Windows-based LAN systems. Multi-user access is available for a small increase in the license fee. Please let us know if you would like a multi-user license for **αlpha**.

1.8 The Integrated Test

The **Integrated Test** and the **Serum Integrated Test** can be used with **αlpha**, including variants of these tests, for example, with **Triple Test** markers in the second trimester instead of the **Quadruple Test** markers. The software provides a full audit trail, including alerts to women who have not attended for the second stage. For more information on the setup needed, monitoring and management features available for the Integrated Test, refer to:

- Section 3.1.6 Cut-offs
- Section 4.1 Data entry

Section 3.11

- Integrated test options

2 General Principles

This section provides you with background information on using the **αlpha** software. It also outlines what you will need to do to get started. The facilities mentioned briefly in this chapter are described in greater detail in other chapters of the manual.

If you are viewing this manual as a PDF file using Adobe® Reader® where you see the "hand" icon you can click on the link to jump to the relevant place in the manual.

2.1 Terms used in this manual

Some of the terms frequently used in **αlpha** are given in Table 1:

Table 1: Terms frequently used in αlpha

Term	Meaning
Data entry screen	The screen where the demographic, clinical information and sample measurements from each patient can be entered, reviewed or modified.
Field	1) Information in the **αlpha** data entry screen is entered into a **field** 2) The location in a record in the **αlpha** database where information is stored
Prompt	The text to the left of the **field** in the data entry screen which gives the meaning of the data is the **prompt**
Batch file	Data on a number of patients (taken, for example from request cards) entered together are stored in a **batch file** or **batch**
Record	Each patient in a **batch file** or in the **αlpha database** is referred to as a **record**
Report	The screening interpretation and results obtained from processing the patient record
Database	Each report is added to the **αlpha database** when the record has been final reported

2.2 Installation

2.2.1 Installing the software

Your computer should conform to the recommendations in *Appendix* R *Operating environment.*

αlpha 8 is supplied on a compact disk (CD). The files are stored in a special compressed format and should not be copied to your computer.

If you are a new **αlpha** user, your **αlpha** distributor will help you install **αlpha** on your computer and set it up according to your requirements. If you are upgrading from an earlier version of **αlpha**, your **αlpha** distributor will help you with the upgrade.

Please do not try to install or upgrade αlpha without assistance from your distributor. If you need to re-install **αlpha** (for example, because of a computer failure) please contact your distributor for help.

Access to the internet is required when **αlpha** is being installed.

2.2.2 Installing the αlpha dongle

The USB dongle provided by your distributor (Figure 1) must be inserted into to a spare USB port on your computer.

The dongle prevents the use of unauthorised copies of **αlpha** and maintains a record of the **αlpha** credits assigned, their date of expiry and the number of credits used (See Section 3.2.5). **αlpha** will not start if the dongle is not attached to your computer. It has no effect on the operation of your computer, and it can be used in conjunction with dongles supplied by most other software manufacturers.

If you plan to install **αlpha** on a server, you need to install a dongle on each workstation on which **αlpha** will be used. You do not need to install a dongle on the server.

Figure 1: USB dongle

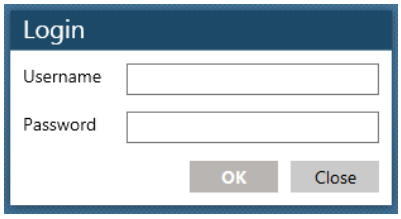
To install the USB dongle:

- Plug the dongle into an available USB port on your computer. It is important to wait for the message "Your new hardware is installed and ready to use" before starting **αlpha**.

2.3 Starting αlpha

αlpha will have been installed on your computer by an approved installer and you will have received training in its use. The installer will assist you in the initialisation of **αlpha**, which must be performed before reports can be produced. The initialisation procedure is described in section 2.4 *Configuration.*

Start **αlpha** by selecting it from the **Programs** menu, or clicking  on your Windows desktop. You will then be prompted for your username and password (See Figure 2)



Enter your username and password in the login dialog box and press Enter or Click OK

Figure 2: Entering username and password

The System Administrator can create a username and password for you if you do not already have one (see section 3.21).

2.4 Configuration

Before you use **αlpha** you will need to configure the software to suit your requirements. Your **αlpha** installer will help you to configure **αlpha**.

First, use **Screen Design** *(see section 3.17)* to select the prompts for the maternal serum (MS) and amniotic fluid (AF) data entry screens. You will then need to specify values for parameters and coefficients relevant to your screening policy and your laboratory. The parameters and coefficients that you specify will depend on your screen designs.

Parameters *(see section 3.1)* are used to specify your screening policy, including screening cut-off levels, when to report risk estimates, concentration units for biochemical markers, and ultrasound machine settings.

Coefficients *(see section 3.2)* are used to define the relationships between:

- gestational age (GA) and expected median values of maternal serum markers and AF-AFP
- crown rump length (CRL) and expected median values of ultrasound markers, such as nuchal translucency
- maternal weight and maternal serum marker MoM values
- biparietal diameter (BPD), crown rump length (CRL), head circumference (HC) and abdominal circumference (AC) measurements and GA.

You can customise **αlpha** further with the options in **Set-up** (*see section 3*). For example, you can choose the way gestational age is entered into **αlpha** and printed on reports. You can also specify your own comments that can be printed on the reports depending on the results of the test.

αlpha checks that you have chosen suitable prompts for the screen designs in order for a report to be produced, and that valid settings are available for all the required parameters and coefficients. **αlpha** displays a message whenever a required parameter or coefficient value has not been set.

2.5 Screening Reports

αlpha is designed to interpret:

i. Maternal serum (MS) and ultrasound markers used in screening for Down's syndrome
ii. MS and history of a previous pregnancy with pre-eclampsia in screening for pre-eclampsia ,
iii. MS alpha-fetoprotein in screening for open neural tube defects.
iv. Amniotic fluid αlpha-fetoprotein and acetyl cholinesterase (AChE) results used in the diagnosis of open neural tube defects.

Clinical information and test results are used to produce reports. This information is stored in a database which you can access in order to review a woman's test results and to monitor the performance of the screening and diagnostic programme. You can tailor **αlpha** to suit your individual requirements.

αlpha is primarily intended for situations in which the information relating to each sample is either available on a screening requisition form, or can be accessed from a data file produced by another computer system (for example, a laboratory information system). Alternatively, you can use a combination of these two approaches. An example of a serum screening requisition form is shown in Figure 3:

DOWN'S SYNDROME AND OPEN NEURAL TUBE DEFECT SCREENING				
Consultant or GP	*DR BROWN*	**ULTRASOUND SCAN**		
		Please use CRL to calculate gestation where possible. Do not use femur length measurement		
PATIENT				
Surname	*JONES*	Ultrasound measurement	*55.4 mm*	
Forename	*JENNY*	Number of fetuses	1	
Date of Birth	*02/03/82*	Scan measurement	*CRL*	
Hospital Number	*1242ZYD*	**1st BLOOD SAMPLE**	Date taken:	07/12/13
Ethnic origin	*Caucasian*	**RESULTS**	AFP (ng/mL):	30.1
CLINICAL DETAILS			uE3 (ng/mL)	2.1
First day of LMP:	*10/09/13*		hCG (miu/mL):	21000
Maternal weight (kg)	*65.2*		Inhibin-A (pg/mL):	210.1
Previous NTD	*None*	**2nd BLOOD SAMPLE**	Date taken:	07/01/14
Previous Down's	*None*	**RESULTS**	PAPP-A (mg/L)	12.11
Previous Pre-eclampsia	*None*	**NT measurement (mm)**	1.2	
Smoker	*No*		Date taken :	07/12/13
Diabetic	*No*		Sonographer:	*DR EVANS*

Figure 3: Screening requisition form

Screening requisition forms are normally processed in batches. The data are entered into the computer using the data entry screen (See Figure 4). The data entry screen consists of a series of **fields** (into which the data is entered) and **prompts** (which give the meaning of the fields).

αlpha requires the following information in order to produce a report:

- patient identification
- maternal age (MS reports only)
- at least one estimate of gestational age
- date of sample
- maternal serum marker or ultrasound marker (MS reports) or AF-AFP level (AF reports)

The data entered are checked and a screening report produced automatically. The screening report produced by the data entered in is shown in Figure 5.

You can enter more information if you wish; for example, gestational age by ultrasound scan, additional screening markers, ethnic group, maternal weight and previous history of Down's syndrome or open neural tube defects. A full list of the available items is given in *Appendix* B *Prompts and their meanings* and further information about data entry is given in Section 4.1.

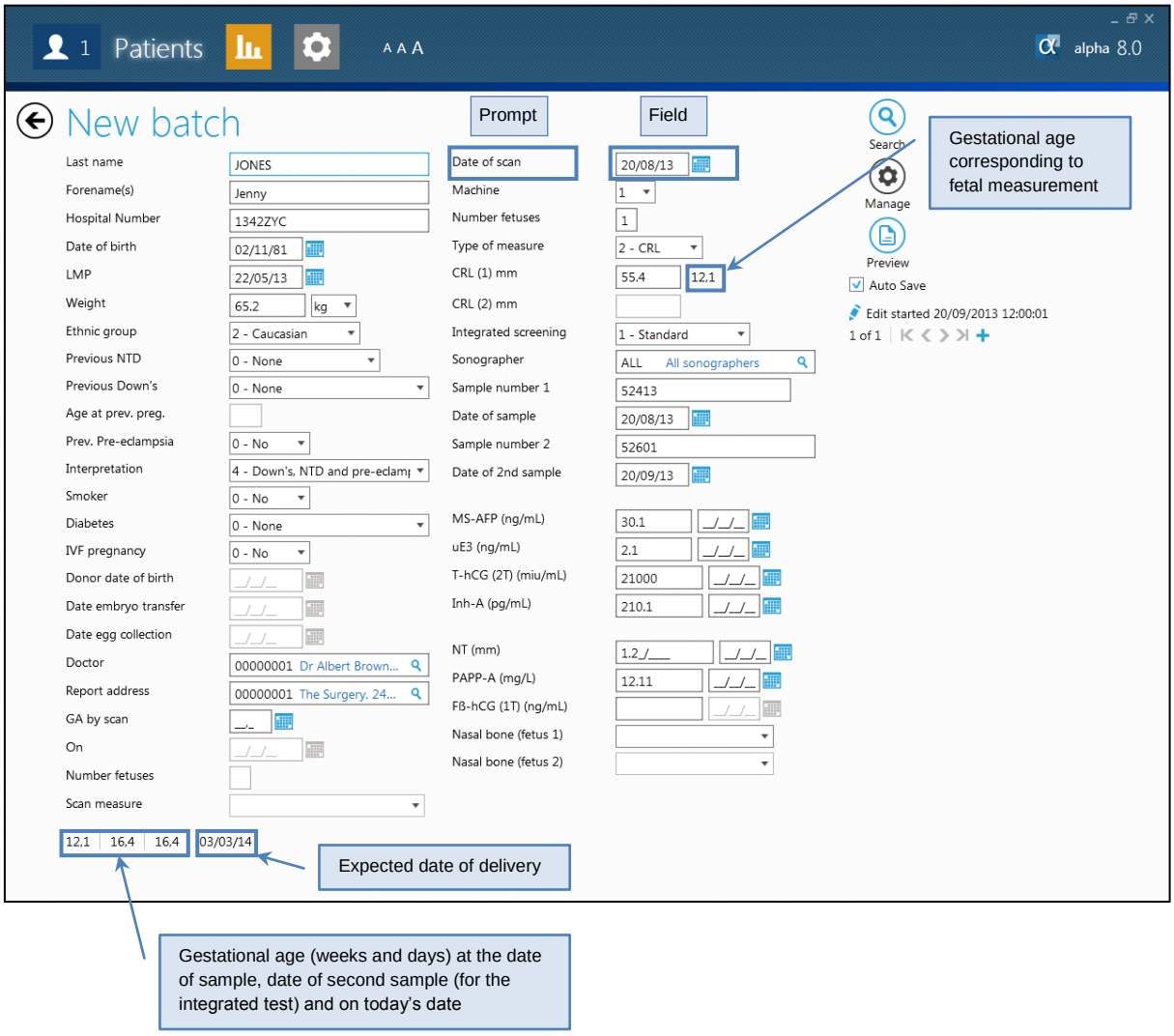


Figure 4: Data entry screen corresponding to Figure 3

Dr Albert Brown MD
The Surgery
24 Park Lane
LONDON
NE3 ZA9

DOWN'S SYNDROME, NEURAL TUBE DEFECT AND PRE.ECLAMPSIA SCREENING

Report dated 08 Jan 14

Last name :	**JONES**
Forename(s) :	**Jenny**
Hospital Number :	1342ZYD
Date of birth :	02/03/82
LMP :	10/09/13
EDD :	20/06/14
Date of sample :	07/12/13
Date of 2nd sample :	07/01/14
Sample number 1 :	52413
Sample number 2 :	52601

CLINICAL DETAILS AND TEST RESULTS

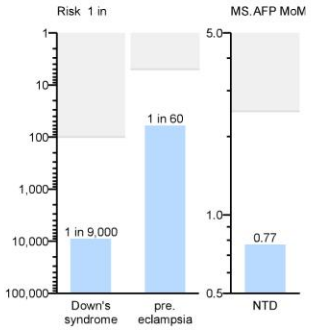
Previous NTD :	None	
Previous Down's :	None	
Prev. Pre.eclampsia :	No	
Insulin dependent diabetes :	None	
Smoker :	No	
Maternal age at EDD :	32 years	
Scan measurement (CRL) :	55.4 mm on 07/12/13	
Gestation at date of 1st sample :	12 weeks 4 days (by dates) 12 weeks 1 days (by CRL scan)	
Gestation at date of 2nd sample :	17 weeks 0 days (by dates) 16 weeks 4 days (by CRL scan)	
Gestation used :	Scan estimate (CRL)	
Weight :	65.2 kg	
Ethnic group :	Caucasian	
MS.AFP level :	30.1 ng/mL	0.77 MoM
uE3 level :	2.1 ng/mL	0.75 MoM
Total hCG level :	21000 miu/mL	1.27 MoM
Inhibin.A level :	210.1 pg/mL	0.96 MoM
Nuchal measurement :	1.2 mm	0.96 MoM
PAPP.A level :	12.11 mg/L	1.10 MoM

If required, a riskometer can be added to provide a graphical visualisation of the risk

INTERPRETATION

Screening result :	**Screen negative**
Risk of Down's :	1 in 9,000 (at term)
Risk of NTD :	1 in 7,000
Risk of Pre.eclampsia :	1 in 60

Comment : Down's risk due to maternal age alone is 1 in 720
Comment : Not in the high risk category for trisomy 18 (risk < 1 in 100)
Comment : Not in the high risk category for trisomy 13 (risk < 1 in 100)



A screen negative result does not exclude the possibility of Down's syndrome, a neural tube defect or pre.eclampsia, because screening does not detect all affected pregnancies

This is an Alpha report

Figure 5: Screening report corresponding to data in Figure 4

2.6 Navigating αlpha

2.6.1 αlpha sections

There are three principal sections in **αlpha**: **Patients** (see Section 4), **Statistics** (see Section 5) and **Setup** (see Section 3). These are selected by clicking on the icons at the top of the screen (Figure 6)

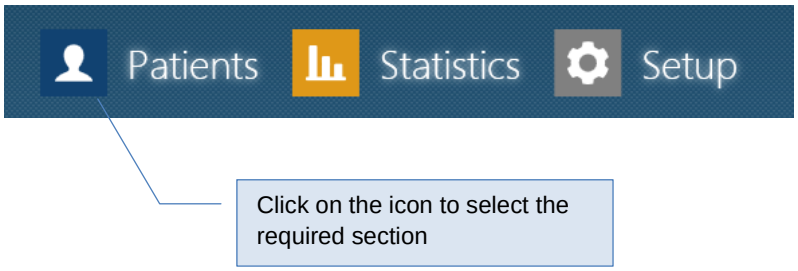


Figure 6: Navigating αlpha using the icons

The principal features in each section are shown in Table 2:

Table 2: Sections in αlpha

Section		Principal features
	Patients	Data entry, reporting, import, search and corrections
	Statistics	Tabulation, median monitoring, regressions
	Setup	Configuration and setup features

Additional screens will be opened as you navigate through **αlpha**. The number of screens open which are associated with each section are shown next to the corresponding icon (Figure 7)

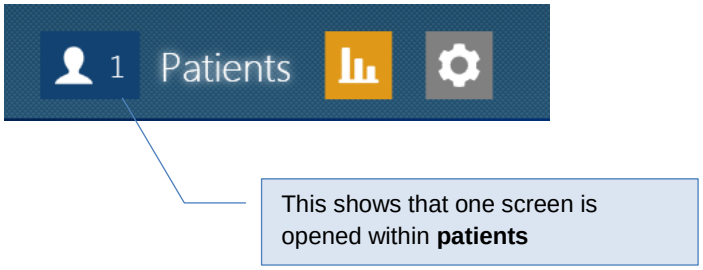


Figure 7: The number of screens associated with a section is shown next to the icon

If you allow the mouse to hover over the icon, it will show a thumbnail of the screens which are open. Clicking on a thumbnail will open that screen (Figure 8). The screen can also be closed by clicking the red cross on the thumbnail.

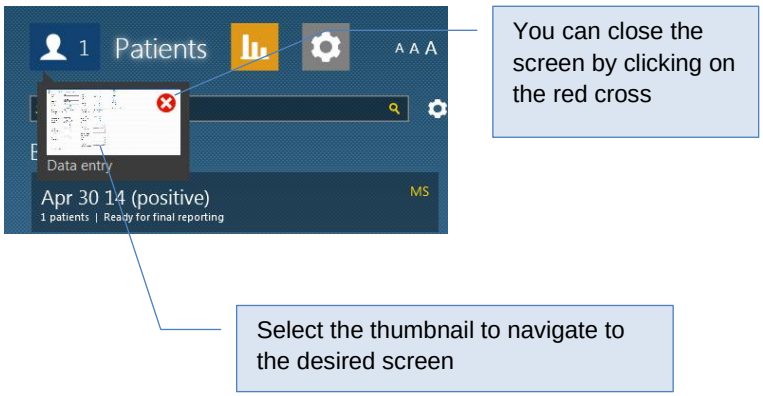


Figure 8: Thumbnails show which screens are open and allow you to navigate and close them quickly

Screens are usually closed by pressing the button at the top left hand corner of the screen. Pressing this will return you to the previous screen.

Navigating within each of the screens is generally by selecting the option required from the list shown by clicking on the button or item required.

2.6.2 Entering dates in αlpha

Dates are entered in the same way throughout **αlpha** (Figure 9). The date separators are automatically provided and only the numbers of the date need to be entered. The day, month and year are all entered as two digits, so for example the 2nd of the month is entered using the digits “02”.

The date is entered in the format specified by your local computer setting. Also, the date separator displayed is the one specified by your local computer setting.

When the date format is day/month/year a date such as 2nd January 1981 would be entered by typing 02 01 81. Pressing displays a calendar from which the date can be selected using the mouse.

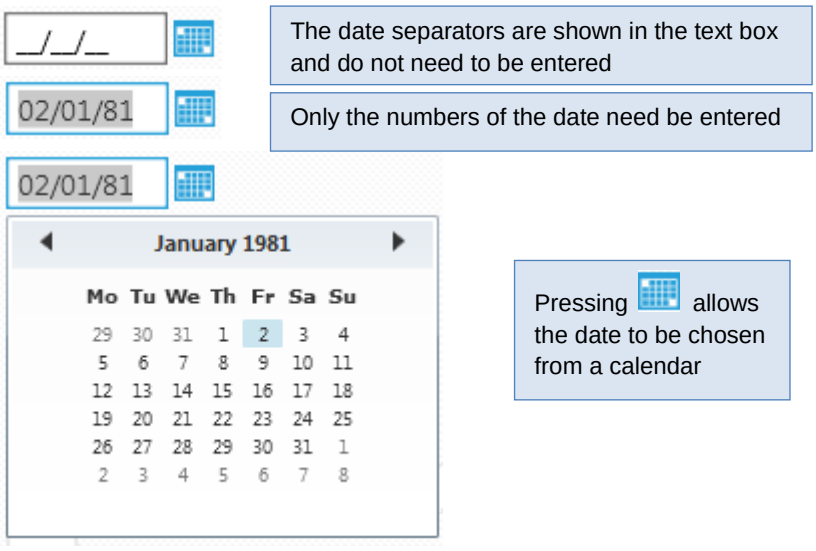
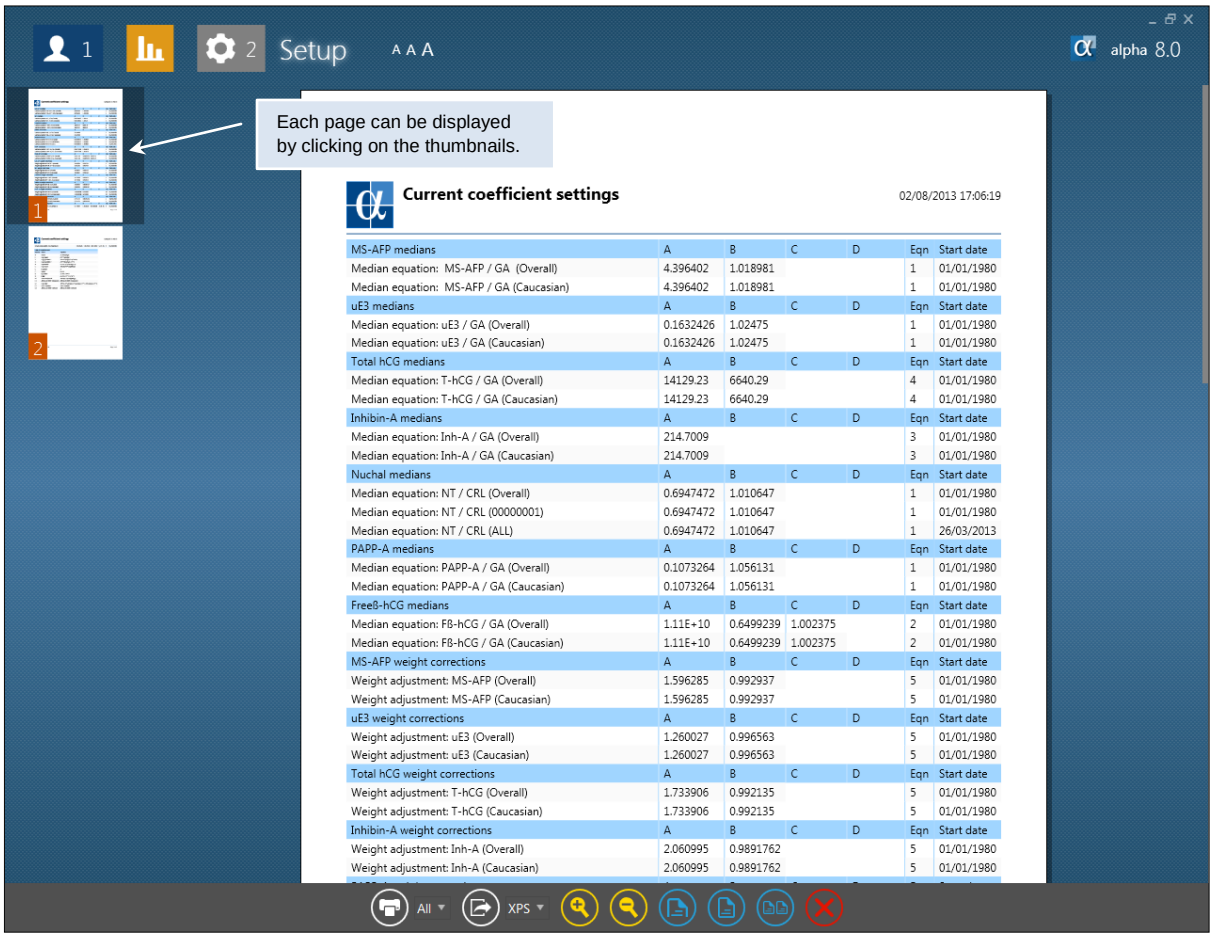


Figure 9: Entering dates

2.6.3 Print preview screen

Throughout **αlpha** results which can be printed are presented in a common format (Figure 10).



MS-AFP medians	A	B	C	D	Eqn	Start date
Median equation: MS-AFP / GA (Overall)	4.396402	1.018981			1	01/01/1980
Median equation: MS-AFP / GA (Caucasian)	4.396402	1.018981			1	01/01/1980
uE3 medians	A	B	C	D	Eqn	Start date
Median equation: uE3 / GA (Overall)	0.1632426	1.02475			1	01/01/1980
Median equation: uE3 / GA (Caucasian)	0.1632426	1.02475			1	01/01/1980
Total hCG medians	A	B	C	D	Eqn	Start date
Median equation: T-hCG / GA (Overall)	14129.23	6640.29			4	01/01/1980
Median equation: T-hCG / GA (Caucasian)	14129.23	6640.29			4	01/01/1980
Inhibin-A medians	A	B	C	D	Eqn	Start date
Median equation: Inh-A / GA (Overall)	214.7009				3	01/01/1980
Median equation: Inh-A / GA (Caucasian)	214.7009				3	01/01/1980
Nuchal medians	A	B	C	D	Eqn	Start date
Median equation: NT / CRL (Overall)	0.6947472	1.010647			1	01/01/1980
Median equation: NT / CRL (00000001)	0.6947472	1.010647			1	01/01/1980
Median equation: NT / CRL (ALL)	0.6947472	1.010647			1	26/03/2013
PAPP-A medians	A	B	C	D	Eqn	Start date
Median equation: PAPP-A / GA (Overall)	0.1073264	1.056131			1	01/01/1980
Median equation: PAPP-A / GA (Caucasian)	0.1073264	1.056131			1	01/01/1980
Freeβ-hCG medians	A	B	C	D	Eqn	Start date
Median equation: Fβ-hCG / GA (Overall)	1.11E+10	0.6499239	1.002375		2	01/01/1980
Median equation: Fβ-hCG / GA (Caucasian)	1.11E+10	0.6499239	1.002375		2	01/01/1980
MS-AFP weight corrections	A	B	C	D	Eqn	Start date
Weight adjustment: MS-AFP (Overall)	1.596285	0.992937			5	01/01/1980
Weight adjustment: MS-AFP (Caucasian)	1.596285	0.992937			5	01/01/1980
uE3 weight corrections	A	B	C	D	Eqn	Start date
Weight adjustment: uE3 (Overall)	1.260027	0.996563			5	01/01/1980
Weight adjustment: uE3 (Caucasian)	1.260027	0.996563			5	01/01/1980
Total hCG weight corrections	A	B	C	D	Eqn	Start date
Weight adjustment: T-hCG (Overall)	1.733906	0.992135			5	01/01/1980
Weight adjustment: T-hCG (Caucasian)	1.733906	0.992135			5	01/01/1980
Inhibin-A weight corrections	A	B	C	D	Eqn	Start date
Weight adjustment: Inh-A (Overall)	2.060995	0.9891762			5	01/01/1980
Weight adjustment: Inh-A (Caucasian)	2.060995	0.9891762			5	01/01/1980

Figure 10: Example of print preview screen

Table 3 gives the purpose of the buttons at the bottom of the Print Preview screen. In some circumstances the buttons have additional uses. (See Section 4.2.3)

Table 3: Purpose of buttons in Print Preview screen

Button	Purpose
	Print the report
	Write the report to an XPS file
	Zoom in
	Zoom out
	View the report with a full page width
	View a full page of the report
	View two pages of the report next to one another
	Close the preview screen

2.7 Files and the αlpha database

Data relating to a batch of screening requisition forms are stored initially in a named file (known as a batch file). When you produce final reports for a batch of requests, the data in the batch file, together with the values calculated by **αlpha**, are automatically merged into the database, and the batch file is deleted.

Separate databases are kept for MS and AF data, but links are created between the two databases for MS and AF results that relate to the same pregnancy. The database allows you to retrieve individual results easily, and to produce statistics for monitoring. In addition, selected records from the **αlpha** database can be exported to other software applications. For example, you might export screening data from **αlpha** to a spreadsheet or statistics package for further analysis.

New batch files are created using **Data Entry** (Section 4.1) or **Import** (Section 4.5). When the batch is closed **αlpha** prompts to save the batch and gives a batch file name based on the current date plus an extra letter. For example, the first file to be created on 11 April 2013 would have the name **Apr 11 13**. The second file would be **Apr 11 13 A**, unless **Apr 11 13** had already been deleted or reported, in which case **Apr 11 13** would be used again. When using **Data Entry** to create a batch file, you can choose an alternative to the default batch file name, if you prefer.

You can also use **Data Entry** and **Import** to add records to an existing batch file, by choosing the file you want to work with from a file selection window.

Some of the options in **αlpha** automatically create another file, based on the data in an existing batch file. For example, if you have chosen to export the final reports for a batch of requests, instead of printing them, **αlpha** will create an export file. In such cases, the name of the file created consists, by default, of the batch file name plus an extension. For example, **αlpha** might give the name MAR1206A.EX1 to an exported report file for the batch file MAR1206A. You can choose another name for the file if you prefer.

2.8 Processing a batch of tests

For most day-to-day purposes you will only need to use a few of the facilities and options available in **αlpha**, namely those relating to the production of reports for the given batch of tests.

The information relating to a batch of tests must first be entered into a file. The information for each batch is usually stored in a new file, but it is possible to add further tests to an existing batch file. You can add data to a batch file in one of the following ways:

- You can enter each item of data manually using the **Data entry** options.
- You can import some or all of the data from another computer system.

Information you enter, whether manually or from a computer file, is automatically checked. Invalid data are not accepted, and you will be asked to confirm extreme or implausible values.

The next step is to create reports. This is a two stage procedure. First, you create test reports and check the reports for data entry errors. Errors are corrected using the **Data entry** option. Once you are satisfied that the data are correct, you can produce final reports and print them or export them. Once final reports have been created, the data are automatically merged into the database. Any changes must be made using **Correct and update** *(see section 4.4)*.

When you create test reports, three other procedures are automatically applied to the data:

1. **Data Validation: αlpha** verifies that the data entered are valid, and that there are sufficient data present to create each report. If any problems are encountered, you can edit the data at that point and continue.
2. **Matching with a report from the same pregnancy: αlpha** checks to see if there are previous reports from the same pregnancy that can be matched to any of the tests being reported *(see section 4.2.1)*. If potential matches are found, you can select whether or not the new report should be linked to any existing previous report. Matches are only offered to reports for the same woman if the previous test was performed in the last 13 weeks. This avoids the possibility of matching tests across different pregnancies.
3. **Matching with a report from an earlier pregnancy: αlpha** checks to see if there are reports from a previous pregnancy for the same woman. If there is and if the user chooses to, **αlpha** will then adjust the serum marker levels to avoid the problem of recurrent false positive pregnancies. 50'59 (*see section 3.1.11*)

It is important to match reports if the second relates to a repeat sample. This is because interpreting a repeat sample without taking into account the marker levels in the previous sample will yield a risk estimate that is incorrect. **αlpha** takes account of the levels in the previous sample when interpreting repeat samples.

αlpha also allows you to match AF reports to MS reports for the same pregnancy.

After you create the test reports, and correct any errors, the next step is to select the **Final report** option. This creates and prints the final reports and then merges the data into the database.

The other options you are likely to use on a regular basis are:

- **Search and print**, used to search for and print copies of already reported results
- **Correct and update**, used to create corrected reports or to reinterpret reports following the addition of extra information such as an ultrasound estimate of gestational age.

2.9 Types of reports

Amniotic fluid (AF) reports are used in the diagnosis of open neural tube defects.

Maternal serum (MS) reports are used in screening for Down's syndrome, pre-eclampsia and for open neural tube defects. Pregnancies at increased risk of trisomy 18, trisomy 13 or Smith-Lemli-Opitz syndrome (SLOS) can also be identified, if you wish.

In cases where the karyotype of the fetus is already known, as a result of an earlier diagnostic procedure such as chorionic villus sampling, you can request an interpretation for open NTD only, provided the **Interpretation** prompt is included in the MS screen design. Note, however, that screening results are regarded as uninterpretable in cases where an amniocentesis has been performed or attempted on or before the date of the blood sample. This is because amniocentesis sometimes causes feto-maternal transfusion, which can increase the maternal serum AFP level.

If the gestational age is less than 15 completed weeks, or an AFP result is not entered for an individual woman, the test is interpreted for Down's syndrome only. In addition, you can request an interpretation for Down's syndrome only, using the **Interpretation** prompt.

When an interpretation for pre-eclampsia is required, the **Interpretation** prompt must be included in the MS screen design. An interpretation for Down's syndrome and pre-eclampsia, or Down's syndrome, open neural tube defects or pre-eclampsia can be requested.

An additional comment is printed on the report when the interpretation is for Down's syndrome or open neural tube defects only.

2.10 Using αlpha in the diagnosis of open neural tube defects

As well as interpreting markers used in screening for Down's syndrome and open neural tube defects, **αlpha** interprets amniotic fluid alpha-fetoprotein (AF-AFP) and acetyl cholinesterase (AchE) results used in the diagnosis of open neural tube defects (NTDs). Most users will use **αlpha** to interpret screening tests, and the major part of this manual is devoted to its use in screening. This section is intended to give an overview of the issues relating to its use in the diagnosis of open NTDs.

Facilities in **αlpha** that relate to screening are designated as **MS** (for maternal serum) and those relating to diagnostic testing as **AF** (for amniotic fluid). Many of the facilities in **αlpha** are provided for both MS and AF. For example, **Screen Design** provides options for designing both MS and AF data entry screens. In most cases, the same general principles apply to the MS and AF options. Where there are differences or special considerations that apply to the AF options, these are discussed below.

Users who do not wish to use the AF options in **αlpha** can disable them by selecting **Hide all AF options** in the **General** section of **User Options** (see Section 3.20.1*)*. To re-enable the AF options, select the same menu item again.

Before using **αlpha** to interpret diagnostic tests, you need to complete the following setup steps:-

- Design an AF data entry screen
- Specify policy settings relating to the diagnosis of NTD
- Provide estimates of the gestation-specific median AF-AFP levels for your laboratory

These tasks are described in the following three sections.

2.10.1 Designing an AF data entry screen

When designing an AF data entry screen, the same general principles apply as to the MS data entry screen *(see section 3.17 for more details)*.
As a minimum, your AF screen design must include the following prompts:-

- **Surname** and **ID code**, **Surname** and **Date of birth**, or **ID code** and **Date of birth**, to serve as identification fields
- An indication of the woman's age (either **Date of birth** or **Age at EDD**)
- **Date of sample**
- Amniotic fluid AFP level (**AF-AFP**). This is used in classifying the diagnostic result as positive, negative, ambiguous or uninterpretable *(see Appendix* A *Rules used in producing reports)*
- At least one estimate of gestational age (GA)

You may wish to include other fields, as appropriate, for example:-

- **Doctor** and **Report address** (or alternatively, **Reports to**)
- **AchE NTD band**. This is used in classifying the diagnostic result as positive, negative, ambiguous or uninterpretable *(see Appendix* A *Rules used in producing reports)*
- **Amnio reason**
- **AF appearance**

2.10.2 Policy settings related to AF-AFP

The policy settings that relate to AF-AFP are specified in **Parameters** *(see section* 3.1*)*. The following settings are required:-

- AF-AFP cut-offs *(see section 3.1.6)*. You can either specify the same cut-off level (in MoM) for all gestational weeks, or gestation-specific cut-offs for 13-15, 16-18, 19-21 and 22-24 weeks. If gestation-specific cut-off values are used, they must increase monotonically with gestational age. Cut-offs in the ranges 2.0-4.0 MoM, 2.0-4.5 MoM, 2.0-5.0 MoM and 2.0-5.5 MoM are accepted for 13-15, 16-18, 19-21 and 22-24 weeks, respectively.
- Units for AF-AFP *(see section 3.1.13)*
- Median reduction factors for AF-AFP *(see section 3.1.9)*. The relationship between median AF-AFP and gestational age is known to be log-linear for 15-24 weeks, but at 13 and 14 weeks the observed median values may be overestimated by a log-linear model [8]. You use this setting to specify the percentage reduction in median AF-AFP for 13 and 14 completed weeks. The reduction at 13 weeks must be greater than or equal to that at 14 weeks. Reduction factors of 0-40% and 0-20% are accepted, for 13 and 14 weeks, respectively. If the median AF-AFP level at 13 or 14 weeks fits a log-linear regression well, specify a reduction factor of zero.

2.10.3 AF-AFP medians

The coefficients of the equation describing the relationship between median AF-AFP levels and gestational age are specified in **Coefficients** *(see section 3.2)*. The general principles are the same as those for maternal serum markers, except that ethnic group-specific medians are not required, nor are medians specific to the method of estimating gestational age (dates or scan).

Coefficients for the median equations may be derived initially by assaying AF-AFP, in your laboratory, for at least 200 amniotic fluid samples, preferably evenly distributed across three or four gestational weeks (between 13 and 24 completed weeks). After tabulating the data according to gestational week, use the **AF-AFP/GA** option in **Regressions** to derive the coefficients *(see section 5.9.1)*.

If, in your judgement, the regression overestimates the median AF-AFP level at 13 or 14 weeks, select the option **Exclude AF-AFP values before 15 weeks 3 days** and generate the regression again. The ratio of the expected (regressed) median AF-AFP level to the observed level at 13 or 14 weeks indicates the appropriate median reduction factor for each week *(see section 2.10.2)*. For example, if the observed median AF-AFP level at 13 weeks is 200 miu/L and the regressed level (after excluding AF-AFP values before 15 weeks 3 days) is 250 miu/L, the appropriate median reduction factor to specify for 13 weeks is 20% (1-200/250).

Once you have interpreted a sufficiently large number of AF samples with **αlpha**, you can use **AF-AFP/GA** in the **Tabulations** and **Median Analysis** options to monitor median AF-AFP MoM values, and to revise your estimates of the gestation-specific AF-AFP levels, should this be necessary *(see section 5.9.4).*

2.11 Computers

All computers running αlpha must conform to the specification in Appendix R.

2.11.1 Moving computer

When αlpha is running in a single user configuration you can move αlpha to another computer with the following procedure. You may require administrator rights on the new computer to follow this procedure:

1. First you must copy the αlpha database to another location such as a memory stick or external disk drive. To do this, select the Database function in the Setup section (See also section 3.6). Browse to the path where you want to copy the database to and provide a filename. When you press Copy αlpha will copy the SQL server database (.MDB) and log files (.LDB) to the location specified.
2. Make a note of the location of the folder containing the αlpha software which is shown in the "About" tile of the alpha Setup section. (This will usually be the folder C:\Program Files\Logical Medical Systems)
3. Close down αlpha
4. Copy the folder identified in step 2 to the Program Files folder on the new computer. It may be necessary to first copy the folder to a memory stick or external disk drive and then copy from here to the new computer.
5. Locate the αlpha 8 installation CD or the .MSI file used to install αlpha 8. The name of this file will be of the type SetupAlpha8.0.xxxxx.yy.msi. (Contact your αlpha distributor if you are unable to find this).
6. On the new computer navigate to location of the αlpha 8 .MSI file and start the installer by double clicking on the .MSI file name.
7. A screen similar to that in Figure 12 will be shown. Select Components and this will install the components necessary to run the αlpha software. Press Close when it has finished.
8. Remove the dongle from the original computer and insert it into a free USB port in the new computer (see section 2.2.2). Please wait until the message "Your new hardware is installed and ready to use" is shown.

9. On the new computer make a shortcut from the desktop to the file alpha.exe in the Alpha subfolder of the folder copied in step 4.
10. Start αlpha from this short cut. A message box stating “Failure to connect to αlpha database” will be shown. Press OK and the SQL Manager screen will be shown (Figure 11).
11. Enter the following details:
    a. In the “Select server” text box, the name of the SQL server running on this computer.
    b. Under “Log on credentials” select the SQL server authentication mode. Uncheck “Windows authentication” to select SQL server authentication and then enter the username and password for SQL server authentication.
    c. Under “Connect to a database”, select “Attach” and then browse to the memory stick or drive containing the αlpha 8 SQL server database (.MDB) and log files (.LDB) created in step 1.
    d. Under “Copy to” browse to the location of the local Microsoft SQL server data folder and provide a file name for the database and log files when they have been copied to the new location.
    e. Under “Database” enter the database name SQL server will use for these files
    f. Press Test connection. If this is successful press OK to complete the process.
    g. Alpha will start and confirm that the process has been successful.

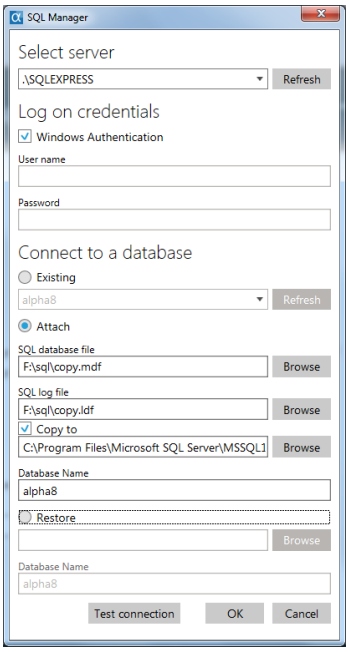


Figure 11: Attaching a new database to alpha

2.11.2 Adding another computer to a multiuser configuration

You can add another computer to a multiuser configuration with the following procedure. You may require administrator rights on the new computer to follow this procedure:

1. Locate the αlpha 8 installation CD or the .MSI file used to install αlpha 8. The name of this file will be of the type SetupAlpha8.0.xxxxx.yy.msi. (Contact your αlpha distributor if you are unable to find this).
2. On the computer you wish to add to the multiuser configuration run the αlpha 8 .MSI installation file
3. A screen similar to that in Figure 12 will be shown. Select Components and this will install the components necessary to run the αlpha software.

4. Make a shortcut from the desktop to the file alpha.exe in the folder on server containing the αlpha 8 software.
5. Insert the dongle into a free USB port in the new computer (see section 2.2.2). Please wait until the message “Your new hardware is installed and ready to use” is shown.
6. Start αlpha from the shortcut.

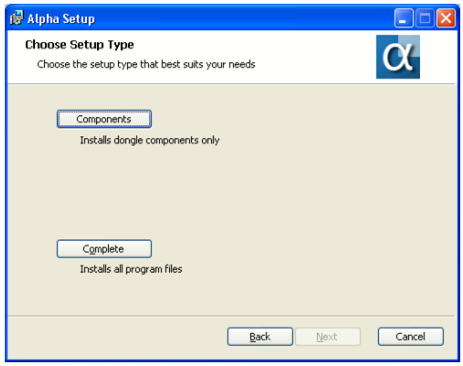


Figure 12: Installing alpha on another computer

3 Set-up

The set-up screen provides you with the options you need to configure **αlpha** to your requirements (See Figure 13). **Note**: *Setup is only accessible to users with security level 4 or higher.* ***Users*** *is only available at security level 6.* The following options are offered:

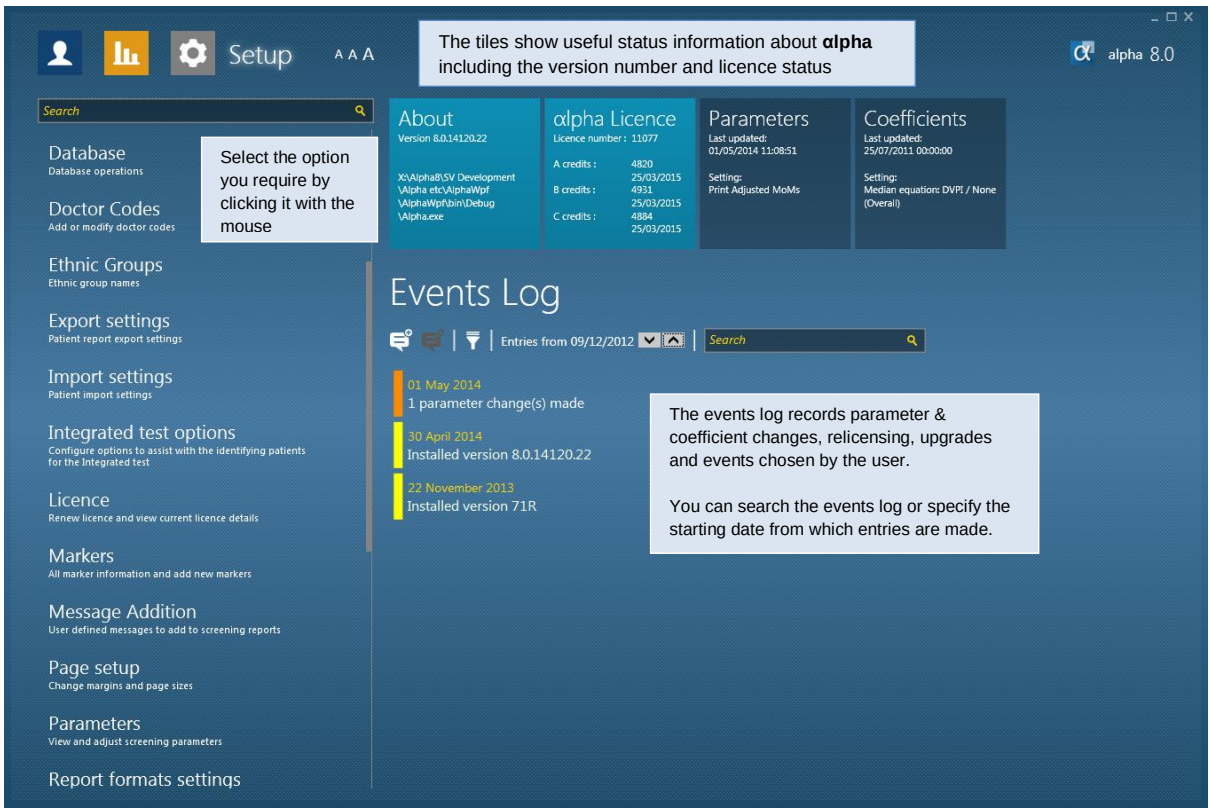


Figure 13: Setup screen

You use **Parameters** to define your screening policy and the way risks are reported. (See section 3.1 and *Appendix* C *Acceptable settings for parameters*)

The equations for expected medians, weight adjustment, and ultrasound gestational ages are defined in **Coefficients** (See Section 3.2.1 and *Appendix* D *Equations used in calculations*).

About provides contact details for Logical Medical Systems and information concerning accreditations.

Address codes, doctor codes and sonographer codes provides a way of allocating codes to addresses, doctors and sonographers to facilitate data entry (*See sections 3.3, 3.6 and 3.18)*

Analyser import allows you to set up how **αlpha** interprets files read from an analyzer. (*See section 3.4).*

Data transfer settings allows you configure the fields you would like to export from the **αlpha** database (*See section 3.5)*

Database allows you to copy the αlpha database to another location. (See section 3.6)

Ethnic groups allows you to specify the names αlpha uses to refer to different ethnic groups (*See section 3.8*)

Export settings configures the files which contain data exported from **αlpha** when a final report is made (*See section 3.9)*

Import settings configures the files which contain the data imported into **αlpha** (*See section 3.10)*.

Integrated test options sets up the features which assist with the management of patients having the Integrated test (*See section 0*)

Use **Licence** to view your **αlpha** licence details, or renew your licence *(See Section 3.12)*

Markers allows you to review the statistical parameters used in **αlpha**, change the marker name and add a new marker (*See section 3.13*).

Message addition allows customised messages to be specified which appear on the **αlpha** report. (*See section 3.14*)

Page setup is used to specify settings (paper size, font size, line spacing, and margins) for four different page styles, that can be associated with different **αlpha** printouts *(see section 3.15)*.

Report format settings allows you to specify the report format files to use for your screening reports (*See section 3.16*).

Screen design allows you to select which fields are used in **αlpha**'s data entry screens and also to define import, export, worksheet and report formats *(see section 3.17)*.

Titles and signature messages specifies the title that appears in the αlpha screen, the top of the screening report and a signature message for the report(*See section3.19*)

User options provides options to further configure **αlpha** according to your requirements. (*See section* 3.20)

With **Users**, you can manage the list of users who can access **αlpha**, by assigning a username, password and security level to each user *(see section 3.21)*. You can also use **Users** to change the password used to log in to **αlpha**. Once a password is assigned to a user, only the user may change the password *(see section 3.21)*.

What-if is an educational tool which allows you to see the effect of changing patient details on the screening result (*See section* 3.22)

Window envelope configures the position of an address on the screening report(*See section* 3.23)

Wipe locks removes any locks put on patient records in batches in cases where αlpha has closed unexpectedly during final reporting.

3.1 Parameters

You use parameters in **αlpha** to specify your screening policy. You can use the **Parameters** screen (Figure 14) to:

- Change the setting of any parameter
- View the current and historical settings for a parameter
- Print current and historical settings for all parameters

The parameters in **αlpha** fall into the following categories:

- adjustment for ethnic group
- NTD & pre-eclampsia background prevalences
- BPD correction factors
- cutoffs
- footnotes
- median equation policies
- AF-AFP median reduction factors (if AF-AFP options are activated).
- printing of risks
- matching for recurrent false-positives
- scan update policy
- units of measurement

αlpha stores historical settings for each parameter, together with the dates on which settings were changed. When reports stored in the database are reprinted, or are accessed for statistical tabulations, **αlpha** ensures that the correct setting is used for each parameter by retrieving the setting that was current on the date of the original report.

The parameters are described in more detail below, and a complete list of the parameters and their acceptable settings is given in *Appendix* C *Acceptable settings for parameters***.** You may not need to set all the parameters, depending on your screen design. **αlpha** displays a warning message if any required parameters are missing.

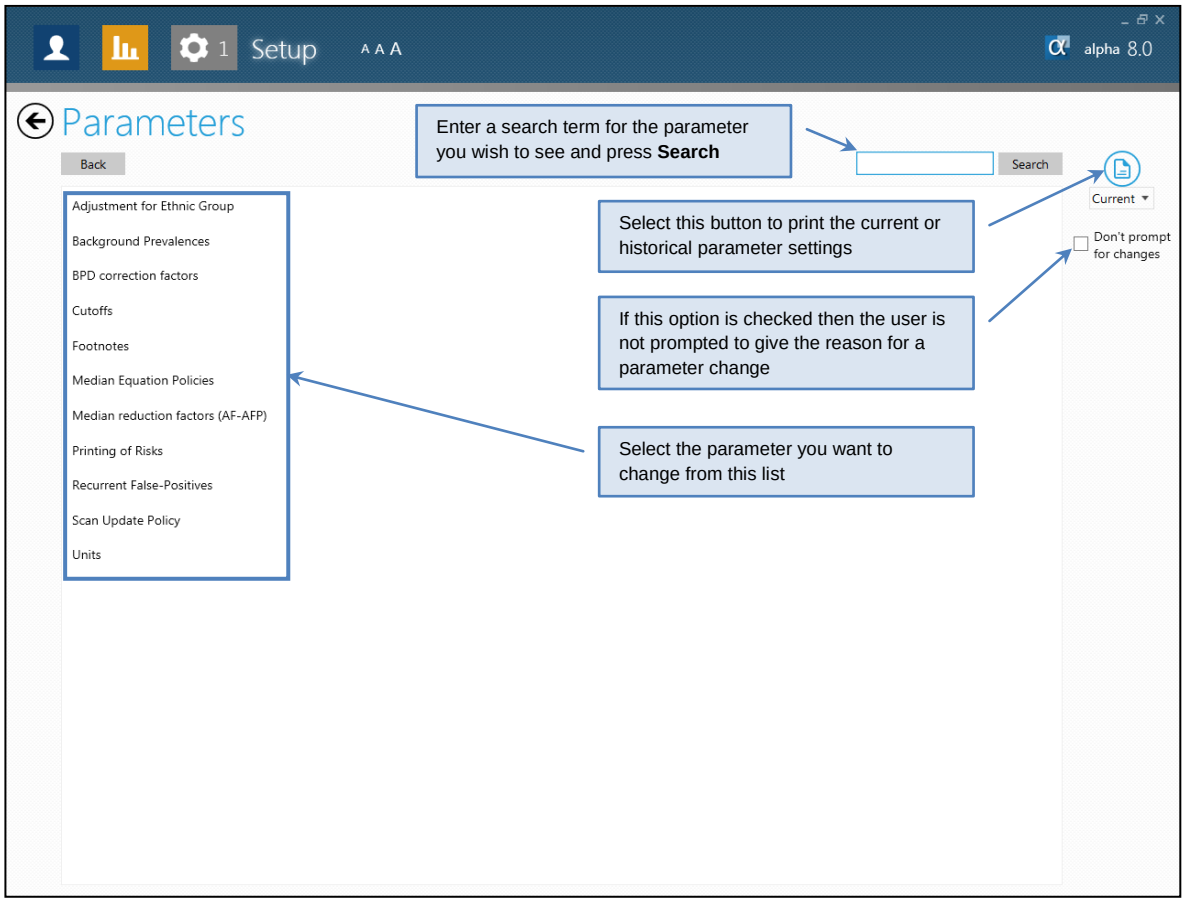


Figure 14 : Parameters screen

3.1.1 Changing parameters

Parameters are grouped in a branching "tree" structure as shown below (Figure 15). Clicking on the sub branches will lead to a place to enter a value for the selected parameter. Some parameters, for example cut-offs, require a numerical value. **αlpha** will prompt you to enter a value as required.

The first time you set a parameter, it will be given a start date of 1 January 1980. Each time you change a setting, the date and time of the change will be used as the start date and time for the new value. If you change a parameter more than once on the same date, the last setting will be used.

When a change has been made to a parameter, **αlpha** displays a window in which you can record your name and a brief comment (Figure 16).

There are no default settings for the parameters in **αlpha**. You need to explicitly set a value for each required parameter.

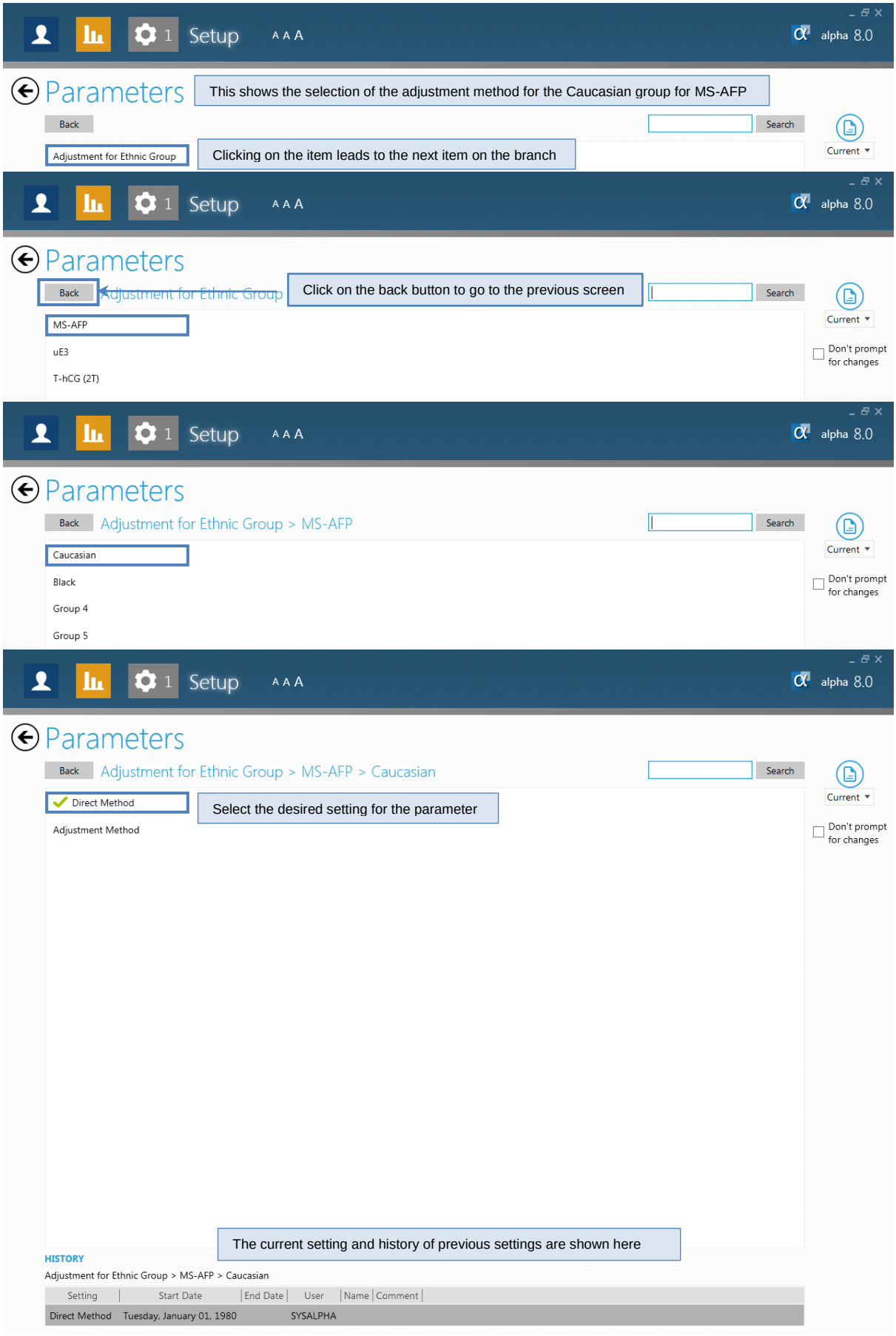


Figure 15: Selecting a parameter value

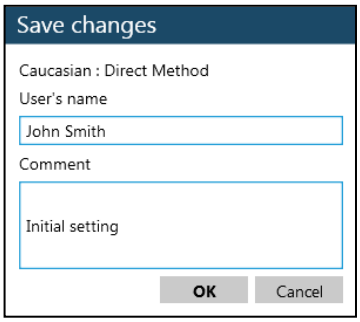


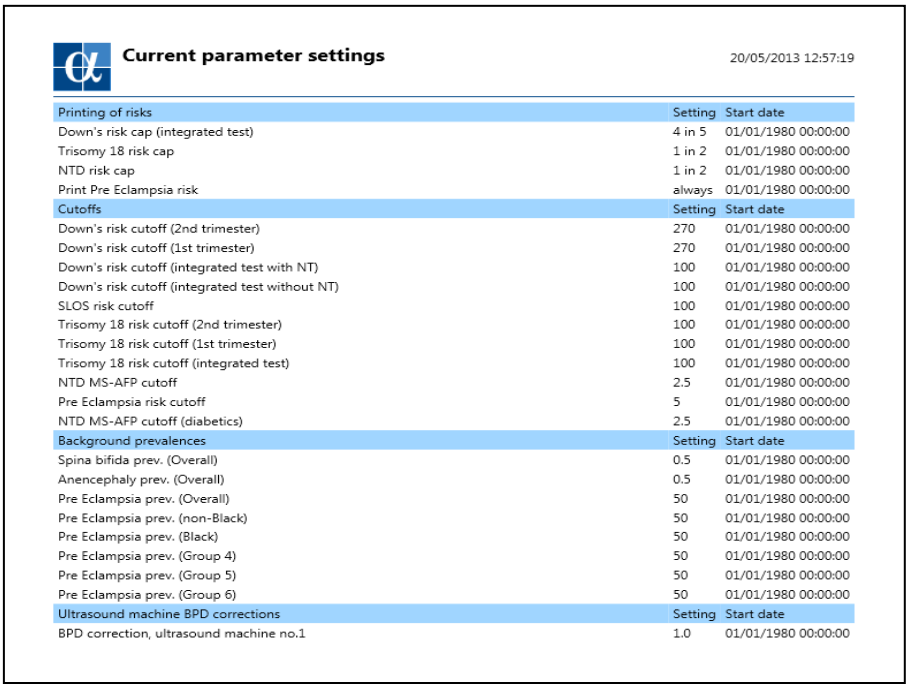
Figure 16: Recording the name of user and reason for change

3.1.2 Printing current and historical parameters

You can print or view a list of current parameter settings and a complete historical list of settings.

Click **Print current** 

to view the current parameter settings (Figure 17). This is helpful when you change one or more settings, to verify that the new settings have been entered correctly. It also provides a summary of your current screening policy.



Current parameter settings 20/05/2013 12:57:19

Printing of risks	Setting	Start date
Down's risk cap (integrated test)	4 in 5	01/01/1980 00:00:00
Trisomy 18 risk cap	1 in 2	01/01/1980 00:00:00
NTD risk cap	1 in 2	01/01/1980 00:00:00
Print Pre Eclampsia risk	always	01/01/1980 00:00:00
Cutoffs	**Setting**	**Start date**
Down's risk cutoff (2nd trimester)	270	01/01/1980 00:00:00
Down's risk cutoff (1st trimester)	270	01/01/1980 00:00:00
Down's risk cutoff (integrated test with NT)	100	01/01/1980 00:00:00
Down's risk cutoff (integrated test without NT)	100	01/01/1980 00:00:00
SLOS risk cutoff	100	01/01/1980 00:00:00
Trisomy 18 risk cutoff (2nd trimester)	100	01/01/1980 00:00:00
Trisomy 18 risk cutoff (1st trimester)	100	01/01/1980 00:00:00
Trisomy 18 risk cutoff (integrated test)	100	01/01/1980 00:00:00
NTD MS-AFP cutoff	2.5	01/01/1980 00:00:00
Pre Eclampsia risk cutoff	5	01/01/1980 00:00:00
NTD MS-AFP cutoff (diabetics)	2.5	01/01/1980 00:00:00
Background prevalences	**Setting**	**Start date**
Spina bifida prev. (Overall)	0.5	01/01/1980 00:00:00
Anencephaly prev. (Overall)	0.5	01/01/1980 00:00:00
Pre Eclampsia prev. (Overall)	50	01/01/1980 00:00:00
Pre Eclampsia prev. (non-Black)	50	01/01/1980 00:00:00
Pre Eclampsia prev. (Black)	50	01/01/1980 00:00:00
Pre Eclampsia prev. (Group 4)	50	01/01/1980 00:00:00
Pre Eclampsia prev. (Group 5)	50	01/01/1980 00:00:00
Pre Eclampsia prev. (Group 6)	50	01/01/1980 00:00:00
Ultrasound machine BPD corrections	**Setting**	**Start date**
BPD correction, ultrasound machine no.1	1.0	01/01/1980 00:00:00

Figure 17: Current parameters settings

Click **Print historical** 

to view the historical list of parameters. This is similar to the list of current settings, except that all the settings ever entered are listed, along with the dates when changes were made. This provides a useful record of changes to your screening policy over time.

3.1.3 Adjustment for ethnic group

Serum marker levels may differ, on average, between women of different ethnic groups. If the screened population is ethnically mixed, **αlpha** can allow for such differences in the marker levels, as well as for differences in weight between women of different ethnic groups[23]. Doing so will help to ensure that the false-positive rate is similar in each group screened. See section 5.13.6 for further information on adjusting for differences between ethnic groups.

For each serum marker, you can choose the **direct** method or the **adjustment** method to allow for differences in the concentration of the marker between different ethnic groups.

If the **direct** method is chosen, **αlpha** will expect to find a separate ethnic group-specific normal median equation and weight correction equation for the selected ethnic group. If ethnic group-specific normal median equations are used it is important to derive weight correction equations from the same population because median weights can differ between ethnic groups.

If the **adjustment** method is chosen, you will need to specify a reference population, whose normal median equation and weight correction equation will be used to calculate MoM values in women of the selected ethnic group. You will also need to specify adjustment factors to allow for differences in the marker levels and in maternal weight, between the selected ethnic group and the reference population. The adjustment factors may be derived from your own screening data or from the scientific literature (*see Appendix Q Suggested factors for adjusting MoM values for differences between ethnic groups.)*

To specify ethnic group adjustment factors, select the desired serum marker and ethnic group under **Adjustment for ethnic group** in the **Parameter settings** screen. Specify a reference population and correction factors for adjusting MoM values for differences in the markers levels and in maternal weight between the specified ethnic group and the reference population.

If the **Ethnic group** prompt is not included in the MS screen design, you do not need to specify the method of adjusting for ethnic group.

3.1.4 Background prevalences

The NTD prevalence parameters specify the background prevalence of open NTD's, in the absence of screening and selective abortion. They are used only in estimating the risk of having a pregnancy with an open NTD. In general, reporting the risk of NTD is not recommended, since the criterion used to categorise a screening result as positive or negative is not the risk, but the AFP level.

If the anencephaly prevalence is unknown, a rate of 95% of the corresponding spina bifida prevalence could be used.[5,40] Prevalence rates for women of different ethnic groups need only be set if you have included the Ethnic group prompt in the MS screen design.

The pre-eclampsia prevalence parameter specifies the background prevalence of pre-eclampsia used to estimate the risk of developing a pregnancy with pre-eclampsia.

3.1.5 BPD correction factors

Ultrasound machine numbers or types (for up to nine machines or types of machine) can be specified for users who wish to enter fetal biparietal diameter (BPD), crown-rump length (CRL), and abdominal circumference (AC) measurements directly, rather than the estimates of gestational age derived from the scan examination.

When fetal ultrasound measurements are entered directly, the machine number must be given. The machine number is used to select the equations for calculating gestational age from the fetal measurements (section 3.2.1.3). It is also used to select a correction factor needed to adjust BPD measurements for the sound velocity assumed (1540 or 1600 m/s) and whether the measurement is made “outer-to-outer” cranial edge or “outer-to-inner”.

When a BPD measurement is recorded, αlpha makes an adjustment according to the value of the BPD correction factor you specify for the corresponding ultrasound machine (*see Appendix* C *Acceptable settings for parameters and Section* 3.1.5).The BPD correction factor allows for differences in the estimated gestational age arising from different methods of BPD measurement (outer-to-inner, or outer-to-outer edge of the cranium) and the sound velocity assumed (1540 or 1600 m/s).

The standard measurement is made outer-to-inner cranial edge, with an assumed sound velocity of 1540 m/s, in which case αlpha makes no adjustment (correction factor of 1.0). When other techniques are used for measuring BPD, αlpha reduces the BPD measurement before using the adjusted BPD measurement in estimating gestational age.

For BPD measured outer-to-outer cranial edge with an assumed sound velocity of 1540 m/s, or outer-to-inner cranial edge with an assumed sound velocity of 1600 m/s, the BPD measurement is reduced by 4% (correction factor of 0.96).

For BPD measured outer-to-outer cranial edge with an assumed sound velocity of 1600 m/s, the BPD measurement is reduced by 7% (correction factor of 0.93).

If you are unsure about which adjustment factor is appropriate in your setting, you may wish to discuss this with your ultrasound department.

3.1.6 Cut-offs

Cut-off levels must be specified for the risk of Down’s syndrome and trisomy 18 in second trimester screening, and for the risk of SLOS and trisomy 13. A cut-off MS-AFP MoM level must be specified for open neural tube defects.

If you intend to use **αlpha** for first trimester screening, you will also need to specify Down’s syndrome and trisomy 18 risk cut-offs for first trimester screening.

If you intend to use **αlpha** for screening with the Integrated Test, you will also need to specify a trisomy 18 risk cut-off for integrated screening, a Down's syndrome cut-off for integrated screening tests that include nuchal translucency (NT) measurement, and a Down's syndrome cut-off for integrated screening tests that do not include NT measurement. Different risk cut-offs are needed for different screening tests because a given risk cut-off (say, 1 in 250) may yield different false positive rates according to the screening test used. For example, if you provide first trimester and second trimester screening, and you wish to achieve a 5% false positive rate for both types of screening, using the same risk cut-off for both tests may not yield the desired results.

If you intend to use **αlpha** with sequential screening, you will also need to specify a first trimester risk cut-off to identify those women with very high risk pregnancies who will not proceed to the Integrated test. A high risk cut-off is used for the first trimester test so there is a low false positive rate. The allowed range of risks for the cut-off is 1 in 10 to 1 in 60.

If you intend to use **αlpha** for screening for pre-eclampsia, you will need to specify a pre-eclampsia risk cut-off.

You only need to set the four gestation-specific AF-AFP cut-offs if you intend to produce AF reports.

3.1.7 Footnotes

You can choose to add a standard message to the bottom of the screening reports. The standard footnote for screen positive reports is:

> *A screen positive result indicates an increased risk of having a pregnancy with Down's syndrome or a neural tube defect. Most women with positive screening results will not have an affected pregnancy*.

The standard footnote for screen negative reports is:

> *A negative screening result does not exclude the possibility of Down's syndrome or a neural tube defect, because screening does not detect all affected pregnancies.*

These footnotes will help to ensure that those reading the screening reports do not confuse 'positive' with 'affected', or 'negative' with 'unaffected'.

The footnotes are altered accordingly if the screening result is for Down's syndrome only or for open neural tube defects only or for Down's syndrome and pre-eclampsia *(see section 2.9)*.

3.1.8 Median equation policies

For serum markers, you can specify that **αlpha** use either a single median equation, regardless of the method of estimating gestational age, or separate median equations for gestational age estimated by ultrasound scan and for gestational age estimated by 'dates' (LMP) or otherwise.

In situations where most pregnancies are dated by one method or the other, a single equation could be used. Where both methods are used in a significant proportion of women, separate median equations are preferred. This is because there may be systematic differences in gestational ages estimated by the two methods, which could lead to differences in the expected median levels at a given gestational age.

This policy can be specified for each marker and each ethnic group in the screened population.

3.1.9 Median reduction factors (AF-AFP)

The relationship between median AF-AFP and gestational age is known to be log-linear for 15-24 weeks, but at 13 and 14 weeks the observed median values may be overestimated by a log-linear model [8]. **αlpha** allows you to specify the percentage reduction in median AF-AFP for 13 and 14 completed weeks.

αlpha increases the proportional reduction daily from 15 weeks and 2 days to 14 weeks and 3 days using the 14 week parameter value, and from 14 weeks and 2 days to 13 weeks and 0 days using the 13 week parameter value.

3.1.10 Printing of risks

The following options are available for controlling the printing of risk estimates for Down's syndrome, open NTD, pre-eclampsia, trisomy 18, trisomy 13 and Smith-Lemli-Opitz syndrome (SLOS) on maternal serum reports:

- For the age-specific and test-specific risks of Down's syndrome, you can choose, separately for reports which are positive and those which are not, whether to print the risk in all cases, never to print the risk, or to print the risk only if the woman's age at her expected date of delivery is equal to or above a specified age. You can also choose to print a message comparing the risk estimate with the age-specific risk.
- For NTD, you can choose to never print the risk, always print the risk, or only print the risk when the screening result is positive.
- For trisomy 18 and trisomy 13, you can choose to never print the risk, or to print the risk when it is equal to or above a specified cut-off risk (see section 3.1.6 Cut-offs). A message can also be printed when the trisomy 18 or trisomy 13 risk is below the cut-off.
- For SLOS, you can choose to never print the risk, to print the risk only if it is equal to or above the specified cut-off, or to print the risk if it is equal to or above the specified cut-off and the risk of Down's syndrome or trisomy 18 is equal to or above the relevant specified cut-off. A message can also be printed when the SLOS risk is below the cut-off.
- For pre-eclampsia, you can choose to always or never print the risk.

The options for controlling the printing of Down's syndrome, open NTD, pre-eclampsia, trisomy 18, trisomy 13 and SLOS risk estimates are described in *Appendix C Acceptable settings for parameters.*

For Down's syndrome, trisomy 18 and trisomy 13, you can specify whether the risk printed is the risk at term or at the time of the test. Second trimester risks are approximately 23% higher than term risk for Down's syndrome [35] and 70% higher for trisomy 18 [3] on account of the selective fetal loss of Down's syndrome and trisomy 18 pregnancies. In the first trimester, the risk of Down's syndrome is approximately 43% higher than at term [35]. For trisomy 13 second trimester risks are approximately 42% higher than term risk and first trimester risks 49% higher on account of the selective fetal loss of trisomy 13 pregnancies. [84]

You can 'trim' risk estimates that are judged to be very low. Risks that are lower than a specified value (1 in x) are printed as **Less than 1 in x** where x is between 20,000 and 1,000,000. Separate settings are provided for trimming the risk in Integrated Tests and non-Integrated Tests.

You can also 'cap' risk estimates that are judged to be very high. Risks that are higher than a specified value (x in y) are printed as **Greater than x in y** where x in y represents a risk between 9 in 10 and 1 in 2 for the risk of Down's syndrome in Integrated Tests, and between 4 in 5 and 1 in 5 for the risk of Down's syndrome in non-Integrated Tests and for the risk of NTD or trisomy 18. Separate settings are provided for 'capping' the risk of Down's syndrome in first trimester, second trimester and Integrated Tests, and for capping the risk of trisomy 18 in all tests.

The range of weeks in which a second trimester test can be interpreted are set with MS 2nd Trimester Interpretation Range. The start of the range can be 14 or 15 completed weeks and the end of the range can be between 19 and 22 completed weeks. If no values are set, the interpretation range is between 14 weeks and 22 weeks 6 days.

The range of weeks in which AF-AFP can be interpreted are set with AF-AFP Interpretation Range. Either 13 to 24 completed weeks or 15 to 21 completed weeks can be chosen. If no values are set, the interpretation range is 15 weeks to 21 weeks 6 days.

A graphical visualisation of the risk can be added with the Print Riskometer option.

If "Print adjusted MoMs" is set to "Adjust" the MoM values on the report will be adjusted in twin pregnancies, IVF pregnancies, for women who smoke and for diabetic women. (See Section 4.2.4)

3.1.11 Recurrent false positives

Women who have had a false-positive screening result in one pregnancy are much more likely to have a one in a subsequent pregnancy than women in general.[50,59] **αlpha** can help to avoid this by adjusting serum marker levels in women who have been screened in a previous pregnancy and who have not had a previous pregnancy with Down's syndrome. You use the **recurrent false-positives** parameter setting to control how **αlpha** identifies such women.

Selecting **Do not adjust** specifies that screening in a previous pregnancy is not taken into account in the interpretation.

Selecting **Strict matching** specifies that women screened in a previous pregnancy are identified on the basis of a matching surname, ID code and date of birth. **Strict matching** will go a long way to avoid false matches, but may mean that such women are not identified in situations where the surname, date of birth, or ID code is not always recorded accurately.

Selecting **Loose matching** specifies that women screened in a previous pregnancy are identified on the basis of a matching surname and ID code, a matching surname and date of birth, or a matching date of birth and ID code. **Loose matching** will increase the chances of identifying such women, but will also increase the chance of a false match.

A previous pregnancy will not be presented as match in the following cases:

- A previous pregnancy has been affected with Down's syndrome or open neural tube defects
- The current pregnancy is a twin pregnancy.
- The previous pregnancy was a twin pregnancy.
- The previous pregnancy was less than 10 months ago
- The previous pregnancy produced an uninterpretable screening result
- The woman was a smoker in one pregnancy but not in the other.
- At least one of the markers measured in the current and previous pregnancy was the same.

See section 4.2.2.2 for further information.

3.1.12 Scan update policy

You use **scan update policy** to control the reinterpretation and reclassification of screening tests from “screen positive for increased risk of Down’s syndrome” to “screen negative” after the addition of ultrasound scan information. You can choose to reinterpret the test always, or to do so only if the new scan estimate of gestation differs from the ‘dates’ estimate by at least a specified number of days (between 1 and 28 days). Tests that are not reinterpreted (because the difference in gestation is too small) are reported with the same screening result (“screen positive”) as the original report, with the addition of a message indicating that the original interpretation remains unchanged.

Restricting the reclassification of screening results in this way will help to avoid giving false reassurance to those women with affected pregnancies who have been given a positive screening result based on dates.[12]

3.1.13 Units

You will need to specify the units of measurement for maternal serum markers, ultrasound markers, AF-AFP and maternal weight for those variables that you have included in the screen design.

3.2 Coefficients

3.2.1 Equations

Coefficients specify the equations (mathematical functions) that define the relationships between:

- gestational age (GA) and the expected median values of maternal serum markers and AF-AFP
- crown rump length (CRL) and the expected median values of ultrasound markers, such as nuchal translucency
- maternal weight and the MoM values of maternal serum markers
- biparietal diameter (BPD), crown rump length (CRL), head circumference (HC), abdominal circumference (AC) measurements and GA

3.2.1.1 Median equations

αlpha uses median equations to estimate the expected median value, in the units of measurement (e.g. ng/mL), of serum markers, ultrasound markers and AF-AFP for a given gestational age.

Where the screened population includes women from different ethnic groups, you can specify ethnic group-specific median equations to allow for differences in serum marker levels between women of different ethnic groups. Alternatively, you can allow for such differences by specifying a median equation for the majority ethnic group (the ‘reference’ group) and correction factors that are used to allow for differences in medians between the reference group and women of other ethnic groups [23].

When specifying coefficients for the first time, it is best to avoid the use of medians in assay package inserts; it is preferable to derive them by assaying samples, possibly in parallel with another laboratory. Preferably, at least 50 samples are used per week of gestation, as follows:

- For second trimester screening, at least 50 samples per week in four gestational weeks, with smaller numbers acceptable in other weeks
- For first trimester screening, at least 50 samples per week in three or more gestational weeks between 10 and 13 weeks.

The form of the median equations is given in *Appendix* D *Equations used in calculations*. A choice of median equations is given for uE3 and inhibin-A and the selection made can be on the basis of how well the equation fits data from your local population.

3.2.1.2 Weight adjustment equations

αlpha uses weight adjustment equations to adjust the MoM values of serum markers for maternal weight. The equations estimate the median MoM value in women of a given weight. A woman's MoM value is divided by the expected median MoM, given her weight, to obtain the weight adjusted MoM, and the adjusted MoM value is used in the interpretation.

Where the screened population includes women from different ethnic groups, you can specify ethnic group-specific weight adjustment equations to allow for differences in weight between women of different ethnic groups. Alternatively, you can allow for such differences by specifying a weight adjustment equation for the majority ethnic group (the 'reference' group) and correction factors that are used to allow for differences in weight between the reference group and women of other ethnic groups [23].

With **αlpha**, you can specify one of two different regression models for weight adjustment: the log-linear model[13], or the linear-reciprocal model.[26] In general, there is little advantage in using one model over the other, and the log-linear model is the one most commonly used. However, you may wish to choose which model to use on the basis of how well each model fits the observed weight-specific MoM values in your own population. You can specify the model used for each serum marker.

The equations for the log-linear and the linear-reciprocal models are given in *Appendix* D *Equations used in calculations.*

3.2.1.3 Equations used to estimate gestational age from fetal ultrasound measurements

These equations are used to estimate gestational age from ultrasound measurements of biparietal diameter (BPD), crown-rump length (CRL), head circumference (HC) and abdominal circumference (AC). You can specify equations for each of nine machines as specified by the ultrasound machine prompt. (See *Appendix* D *Equations used in calculations* for more information).

When a BPD measurement is recorded, **αlpha** makes an adjustment according to the value of the BPD correction factor you specify for the corresponding ultrasound machine (see *Appendix* C *Acceptable settings for parameters* and *Section* 3.1.5 *BPD correction factors*).The BPD correction factor allows for differences in the estimated gestational age arising from different methods of BPD measurement (outer-to-inner, or outer-to-outer edge of the cranium) and the sound velocity assumed (1540 or 1600 m/s).

3.2.2 Overview of Coefficients Screen

You access the Coefficient screen (Figure 18) from the Set-up screen (Section 3). Like the parameter settings, coefficients are grouped in a branching "tree" structure (Figure 19). Clicking on the sub branches will lead, at the end of each branch, to the individual equations with their coefficient settings (Figure 20). The example shows the coefficients (A and B) of the equation that **αlpha** uses in estimating the expected median level of MS-AFP given a woman's gestational age (GA). The table at the bottom of the screen shows the different values assigned to the coefficients over different time periods.

You can use the Coefficient Settings screen to:

- Change the values of the coefficients of any equation
- For uE3 and inhibin change the type of median equation (See *Appendix* D *Equations used in calculations*)
- Record details of the change (who changed the coefficients, and the reason for the change)
- View current and historical values for the coefficients of an equation
- Print current and historical values for all coefficients
- Evaluate the expected values yielded by an equation, given its current coefficient values (prints a table showing the expected marker level for a given GA, the expected MoM value for a given weight, or the expected GA for a given CRL, BPD, HC or AC measurement)
- Specify sonographer-specific medians for ultrasound markers such as nuchal translucency, to allow for systematic differences that may exist between sonographers

Appendix D *Equations used in calculations* shows the equations **αlpha** uses in calculations. Use the Regression options (see section 5.9) to obtain values of the coefficients for a regression equation corresponding to a given set of observed values.

As with parameters, you may not need to set all the coefficients, depending on your screen design and parameter settings. **αlpha** displays a warning message if any required coefficients are missing. There are no default settings for the coefficients – you need to specify the values of all required coefficients.

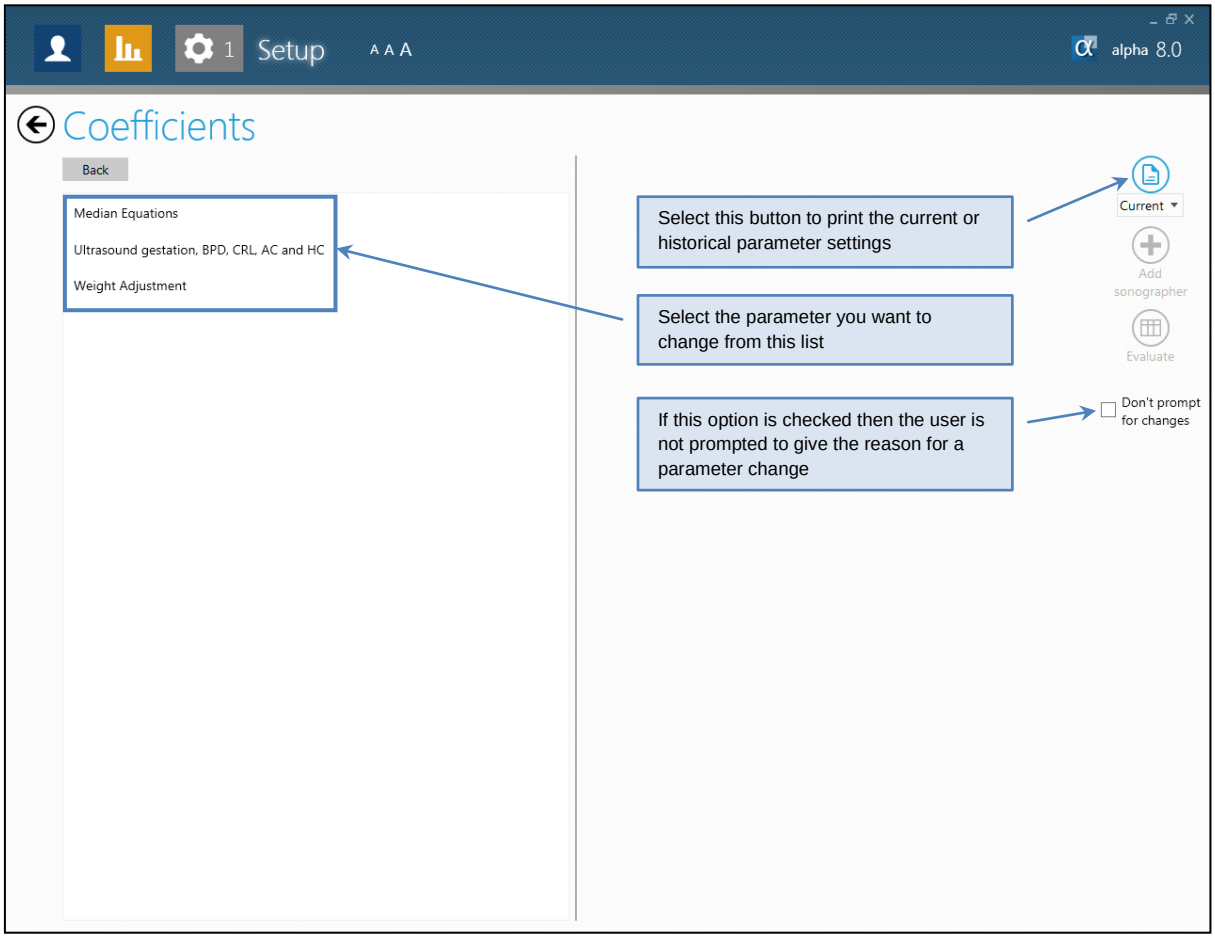


Figure 18: Coefficients screen

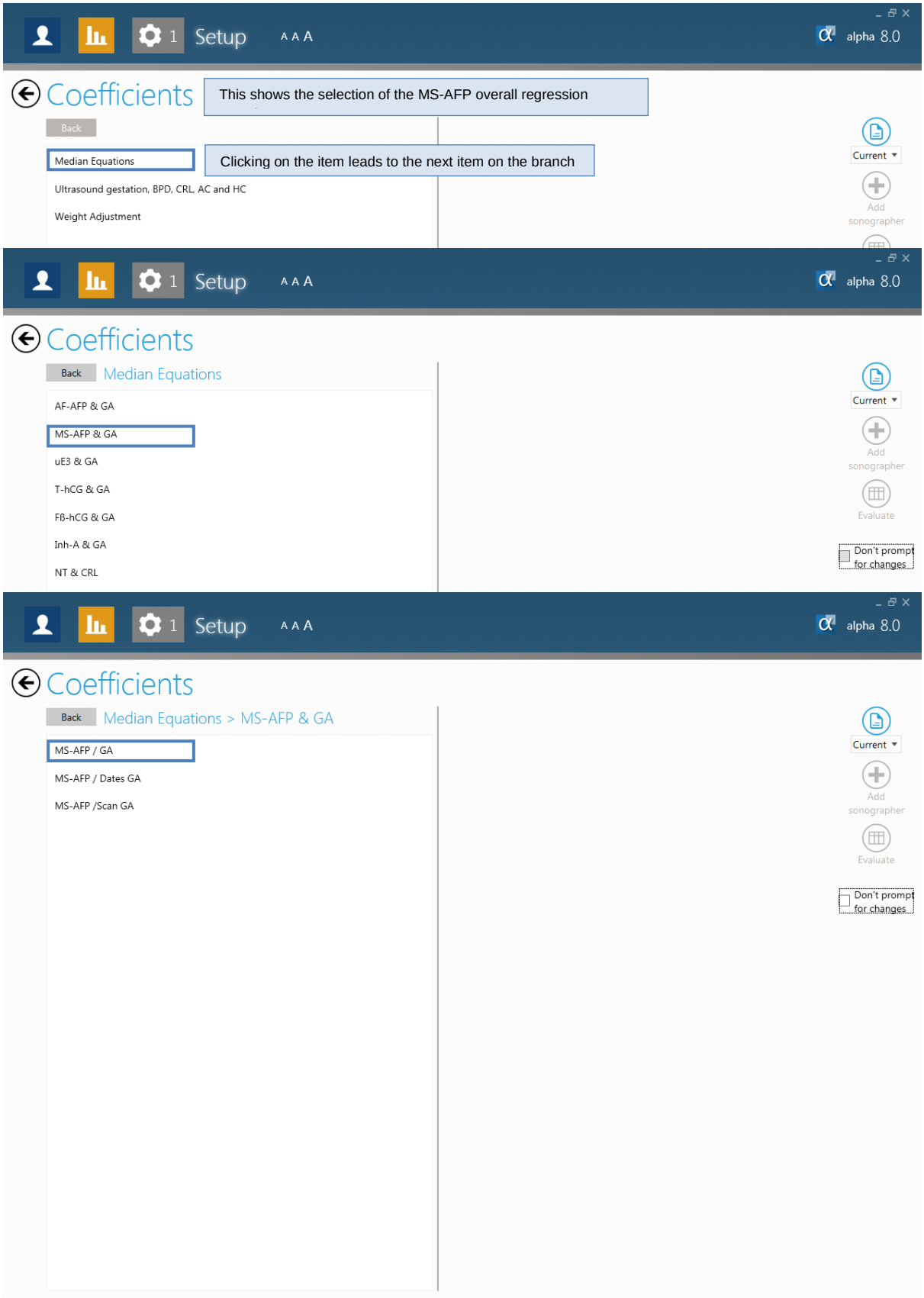


Figure 19: Coefficients screen - selecting option

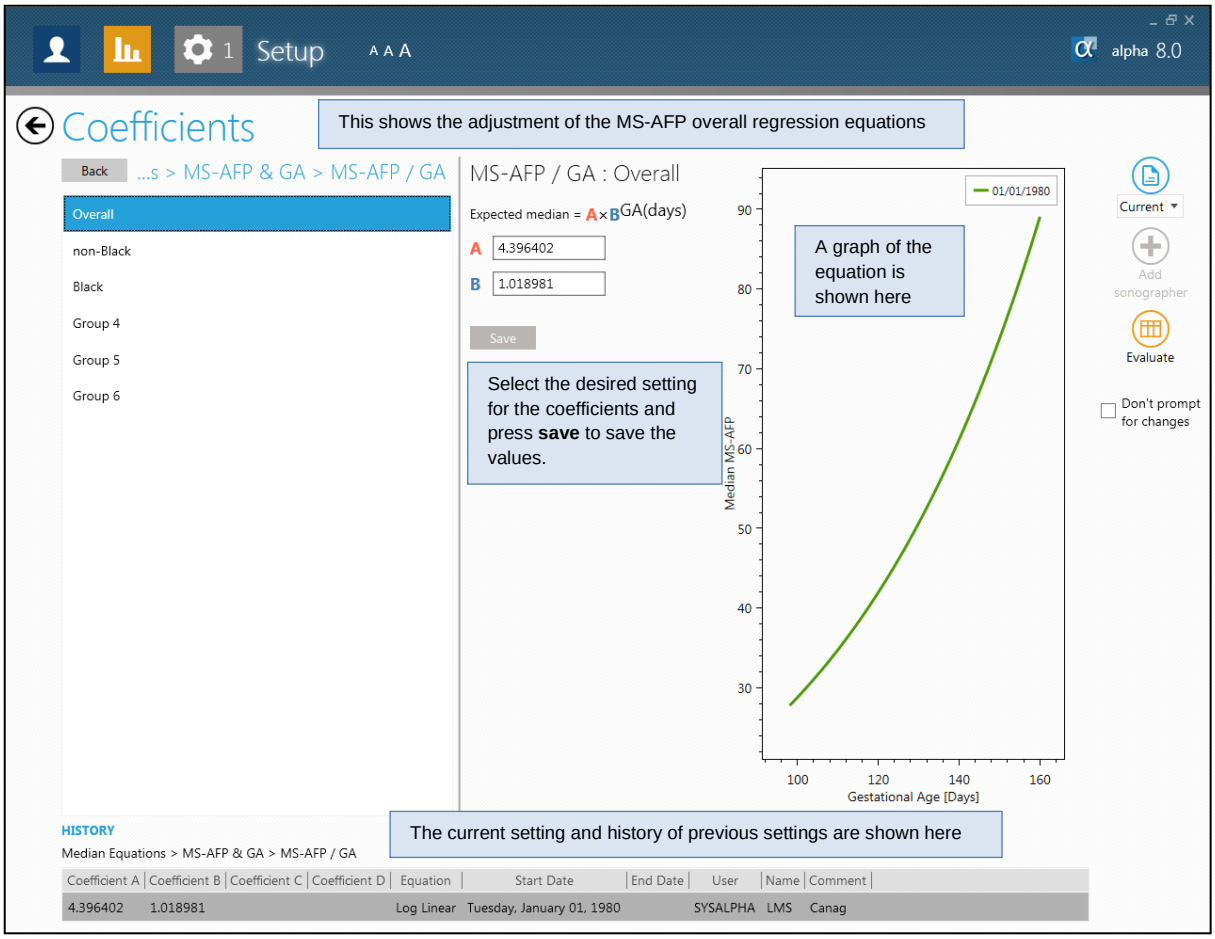


Figure 20: Coefficients – changing values

3.2.3 Changing coefficients

You can change coefficient settings by editing them in the Coefficients screen. (See Figure 20) **αlpha** stores historical settings for each coefficient and the date on which each value was changed. When reports stored in the database are reprinted, or accessed for tabulations, **αlpha** ensures that the correct value is used for each coefficient by retrieving the values that were current at the date of the original report. Coefficients can also be updated without being typed in using the Tabulation and Regressions options (See Section 5.9.4).

Not all coefficients will require setting, and this will depend on your screen design. A full description of the available coefficients is given in *Appendix* D *Equations used in calculations*

For maternal serum markers, coefficients for up to three normal median equations may be given for each ethnic group, according to the median equation policy you have specified (Figure 21). See *section* 3.1.8 *Median equation policies* for more information on specifying median equation policies.

If you wish to specify a sonographer-specific regression equation relating NT to CRL select NT & CRL, press the ⊕ **Add Sonographer** button and select the sonographer from the list. The coefficients for this sonographer can then be entered.

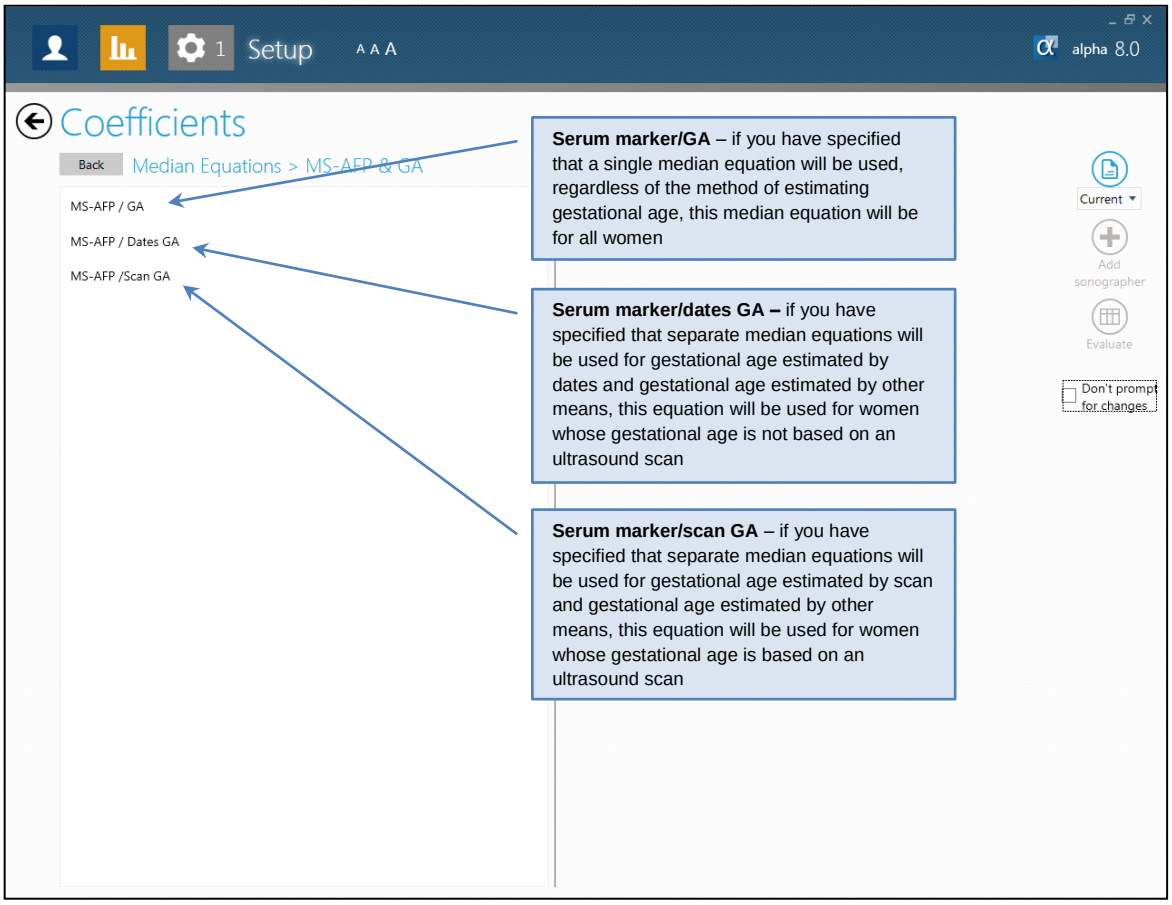


Figure 21: Coefficient and median equation policy

There is a choice of regression equations for the median equations for uE3 or inhibin-A. To choose the equation, select the item you wish to change and press the "Change equation" button and select the new equation from the options given (Figure 22).

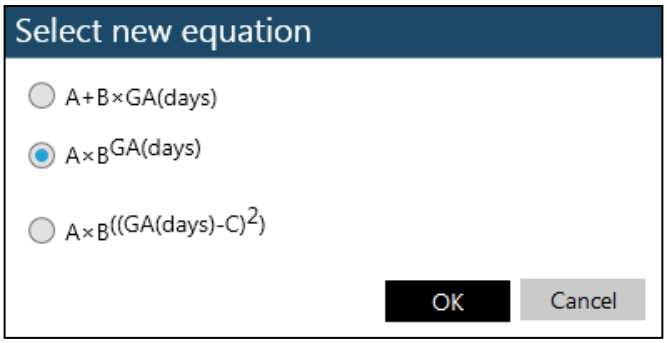


Figure 22: Select equation for uE3

Weight adjustment equations for maternal serum markers may be specified separately for different ethnic groups (Figure 23). To choose a different regression equation, select "Change" and make a selection from the options given (Figure 24).

Equations used to estimate gestational age from ultrasound measurements may be specified for up to nine ultrasound machines or centres (Figure 25). To choose a different regression equation, select "Change" and make a selection from the options given (Figure 26).

The first time you choose a setting for each coefficient it will be given a start date of 01/01/1980. Each time you change a setting, the date and time of the change will be used as the start date.

You will need to enter acceptable values for all the required coefficients before you can create reports.

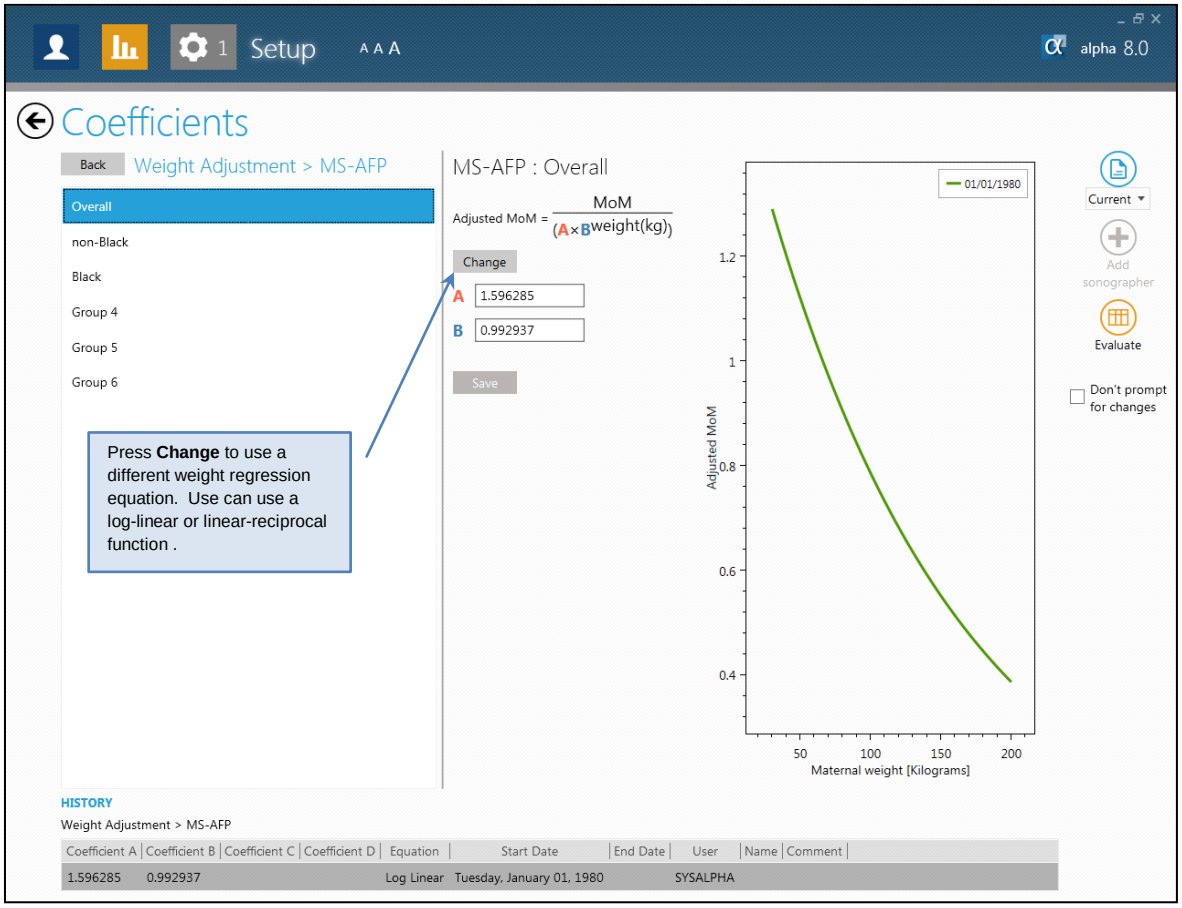


Figure 23: Selecting weight adjustment equations

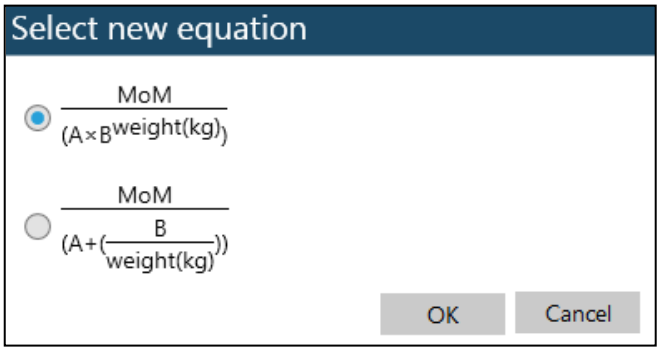


Figure 24: Select weight adjustment equation

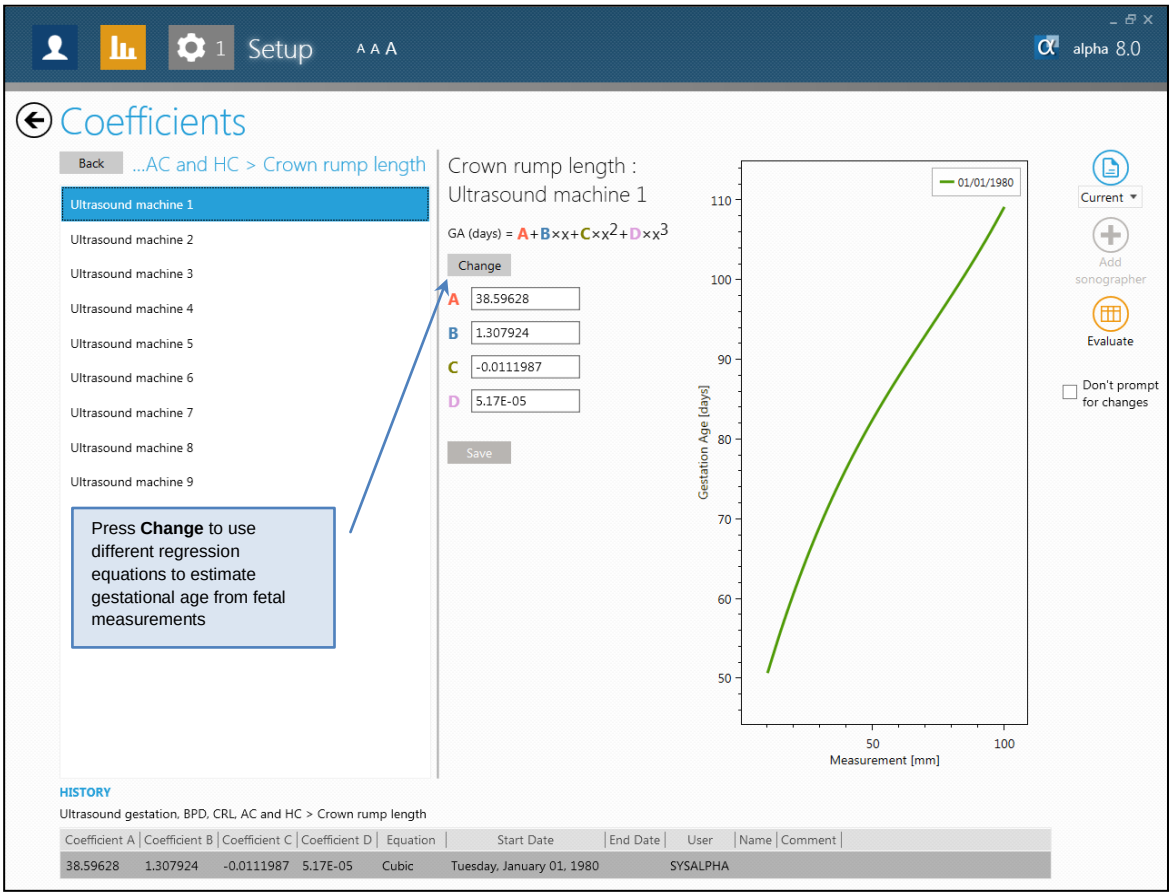


Figure 25: Equations for estimating GA from fetal measurements

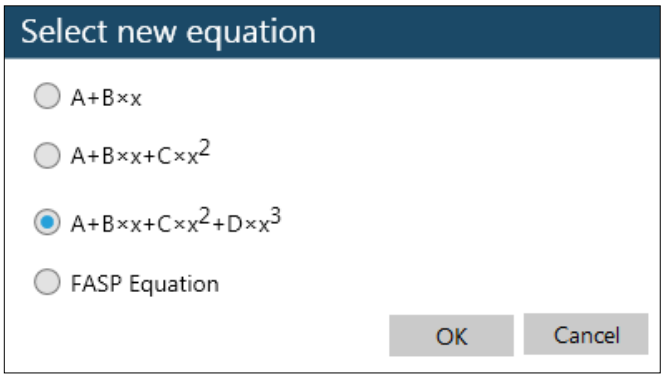


Figure 26: Select new ultrasound equation

3.2.4 Evaluating coefficients

Each time you change coefficient values, select **Evaluate coefficients**  to check that the changes you made are acceptable. This produces a table (Figure 27) showing expected values for the coefficients entered. Examining these tables is a useful safeguard against entering incorrect values for the coefficients of median or weight adjustment equations, and for equations used to estimate GA from fetal ultrasound measurements.

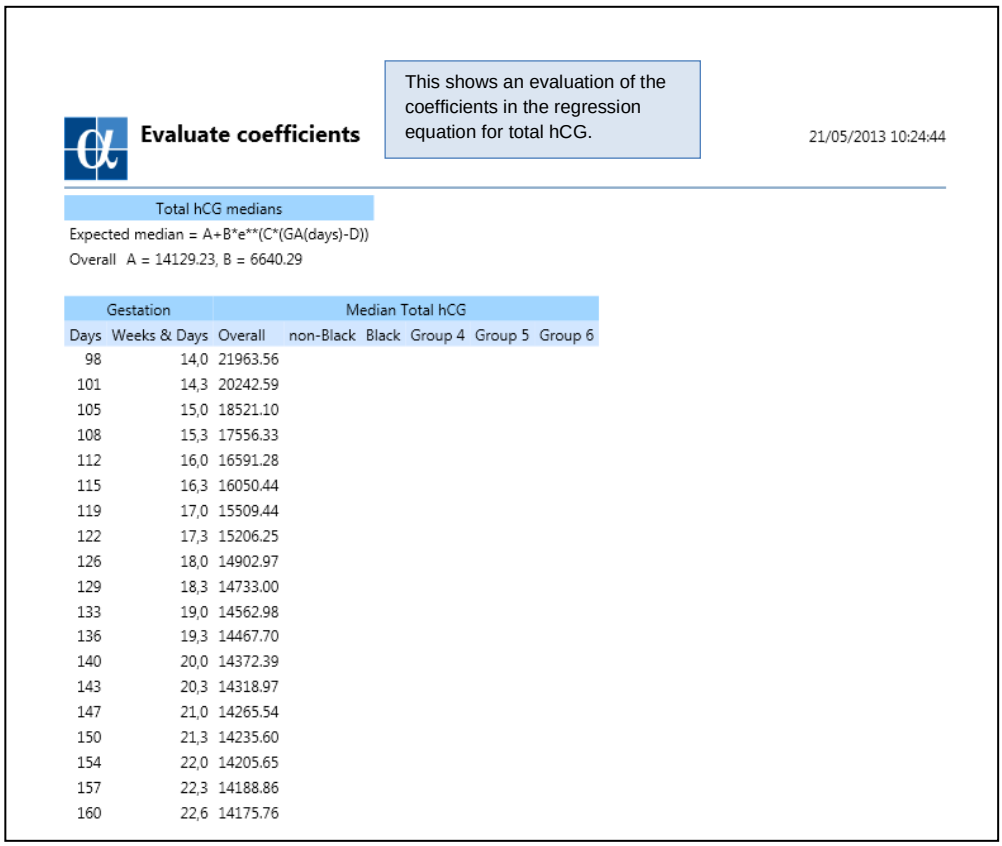


Figure 27: Evaluate coefficients

3.2.5 Current and historical coefficient values

You can print or view a list of current coefficients and a complete historical list of settings.

Click **Print current** 

to view the current coefficient settings (Figure 28). This is helpful when you change one or more settings, to verify that the new settings have been entered correctly.

Click **Print historical** 

to view the historical list of coefficients. This is similar to the list of current settings, except that all the settings ever entered are listed, along with the dates when changes were made. This provides a useful record of changes to your coefficients settings over time.

MS-AFP medians	A	B	C	D	Eqn	Start date
Median equation: MS-AFP / GA (Overall)	4.396402	1.018981			1	01/01/1980
uE3 medians	A	B	C	D	Eqn	Start date
Median equation: uE3 / GA (Overall)	0.1632426	1.02475			1	01/01/1980
Total hCG medians	A	B	C	D	Eqn	Start date
Median equation: T-hCG / GA (Overall)	14129.23	6640.29			4	01/01/1980
Inhibin-A medians	A	B	C	D	Eqn	Start date
Median equation: Inh-A / GA (Overall)	214.7009				3	01/01/1980
Nuchal medians	A	B	C	D	Eqn	Start date
Median equation: NT / CRL (Overall)	0.6947472	1.010647			1	01/01/1980
Median equation: NT / CRL (ALL)	0.6947472	1.010647			1	26/03/2013
PAPP-A medians	A	B	C	D	Eqn	Start date
Median equation: PAPP-A / GA (Overall)	0.1073264	1.056131			1	01/01/1980
Free ß-hCG medians	A	B	C	D	Eqn	Start date
Median equation: Fß-hCG / GA (Overall)	1.11E+10	0.6499239	1.002375		2	01/01/1980
MS-AFP weight corrections	A	B	C	D	Eqn	Start date
Weight adjustment: MS-AFP (Overall)	1.596285	0.992937			5	01/01/1980
uE3 weight corrections	A	B	C	D	Eqn	Start date
Weight adjustment: uE3 (Overall)	1.260027	0.996563			5	01/01/1980
Total hCG weight corrections	A	B	C	D	Eqn	Start date
Weight adjustment: T-hCG (Overall)	1.733906	0.992135			5	01/01/1980
Inhibin-A weight corrections	A	B	C	D	Eqn	Start date
Weight adjustment: Inh-A (Overall)	2.060995	0.9891762			5	01/01/1980
PAPP-A weight corrections	A	B	C	D	Eqn	Start date
Weight adjustment: PAPP-A (Overall)	-0.0049946	64.95892			10	01/01/1980
Free ß-hCG weight corrections	A	B	C	D	Eqn	Start date
Weight adjustment: Fß-hCG (Overall)	2.375735	0.9876558			5	19/01/2010
GA from biparietal diameter	A	B	C	D	Eqn	Start date
Biparietal diameter / GA (Machine 1)	52.33097	1.456614	0.0110454	-3.54E-05	9	01/01/1980
GA from crown-rump length	A	B	C	D	Eqn	Start date
Crown-rump length / GA (Machine 1)	38.59628	1.307924	-0.0111987	5.17E-05	9	01/01/1980

Figure 28: Current coefficients

3.3 Address codes

Address codes provide a way of recording the destination addresses of reports using a code to represent each address. A similar facility is provided for recording the names of doctors (Section 3.6 and sonographers (Section 3.18 Sonographer codes). Using codes reduces data entry time and helps reduce errors. The codes used may be up to eight characters long.

The address codes screen (Figure 29) provides facilities for viewing, editing and deleting stored addresses and adding new addresses.

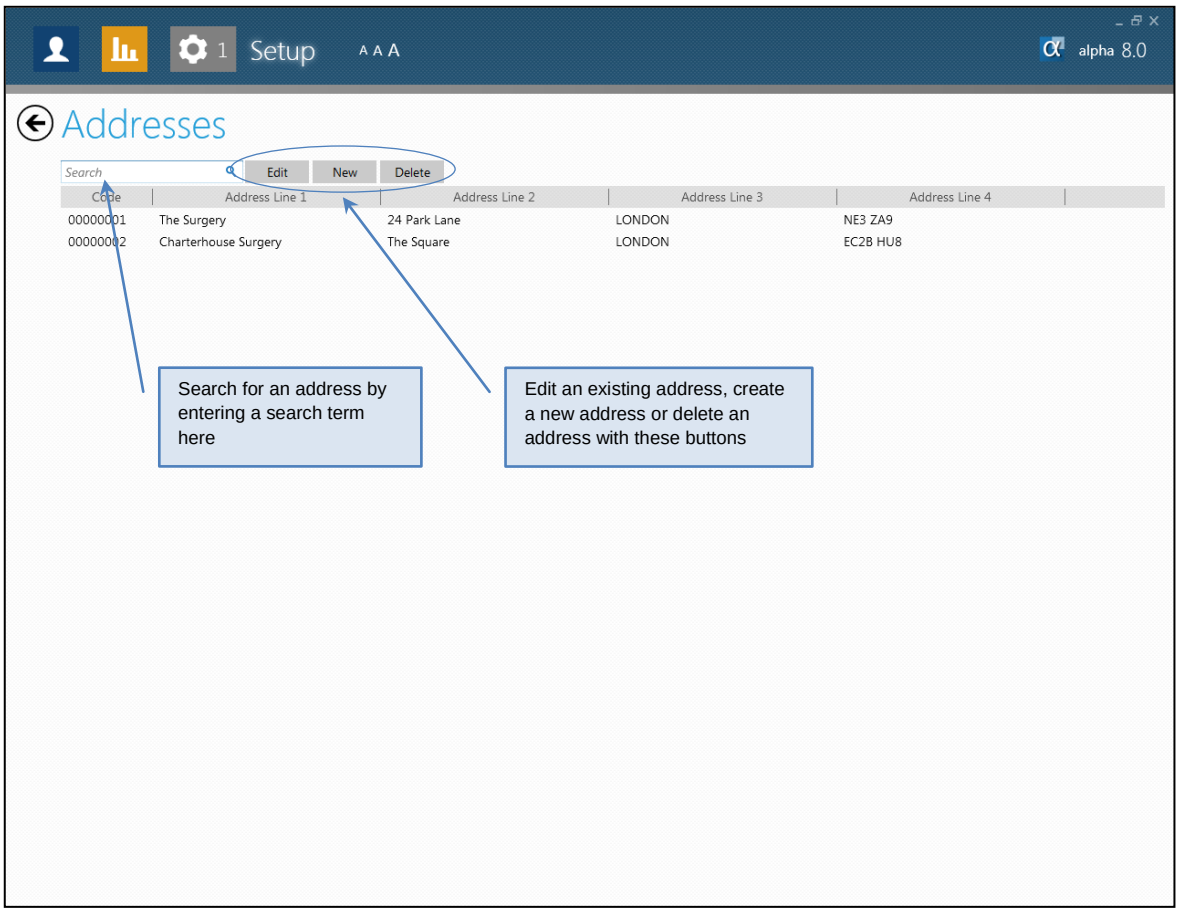


Figure 29: Addresses screen

3.4 Analyser import

3.4.1 Overview

Text files containing analyte measurements from an analyser or laboratory information system can be imported into **αlpha** and the measurements from the file stored with the corresponding patient record in an unreported batch file.

Each qualifying line of the file must contain one or more analyte measurements together with a code such as a sample ID which is used to identify the patient from whom the measurements were taken. When the file is imported into **αlpha** the patient record containing the same code is identified and the analyte measurements added to that record.

The **Analyser Import** screen provides a facility which describes the format of these files for each of the analytes which can be entered into **αlpha**. The files are read into **αlpha** using the Import facility described in section 4.5.

The meaning of each of the items in the Analyser import screen is given in Table 4.

Table 4: Meaning of terms in Analyser Import screen

<table>
<tr><th>Item</th><th>Meaning</th></tr>
<tr><td>File path and mask</td><td>Path and filename of file containing the measurements

If required, a mask can be used to specify the name of the file to be used. The default import filename is given by replacing the mask characters in the following way:

<table>
<tr><th>Mask character</th><th>Replaced by</th></tr>
<tr><td>#</td><td>Numeric digits</td></tr>
<tr><td>DD</td><td>Day number</td></tr>
<tr><td>MM</td><td>Month number</td></tr>
<tr><td>YYYY</td><td>4 digit year</td></tr>
<tr><td>YY</td><td>2 digit year</td></tr>
</table>

Examples:

<table>
<tr><th>Masked filename</th><th>Filename presented as default</th></tr>
<tr><td>AFP<##>B.TXT</td><td>If the last filename matching the mask is AFP04B.TXT:

AFP05.TXT</td></tr>
<tr><td>UE3<DDMMYYYY>A.TXT</td><td>If the date is 22 May 2013:

UE322052013A.TXT</td></tr>
</table>
</td></tr>
<tr><td>Header lines in file</td><td>Number of header lines in the file before the start of the data</td></tr>
<tr><td>Field number for sample ID</td><td>Field number in the file that holds the sample ID

The position of the sample ID in each line of the file. If the sample number is the first field this value should be set to 1, or if the second field that value should be set to 2 and so on.</td></tr>
<tr><td>Field number for result</td><td>Field number in the file that holds the sample ID

The position of the result in each line of the file. If the result is the first field this value should be set to 1, or if the second field that value should be set to 2 and so on.</td></tr>
<tr><td>ASCII code for field separator</td><td>The ASCII code that defines the character that separates items of data in each line of the file. Set this value to zero for one or more spaces.

For example, 44 for a comma “,”.</td></tr>
<tr><td>Decimal separator</td><td>Decimal separator

For example, “.” or “,”.</td></tr>
<tr><td>Result scaling factor</td><td>The factor by which analyte results in the file are multiplied before saving in the batch.

For example, 100.0 or 0.01. Numeric results in the file are scaled by this number.</td></tr>
<tr><td>Lower assay limit</td><td>If the analyte result is less than this value, the limit is entered into the patient record preceded by “<”.

For example, if the assay limit is 1.0 and the value read from the file 0.9 the value stored in the patient record is “<1.0”.</td></tr>
<tr><td>Quotation character</td><td>If the specified character delimits a sample ID or result in the file it is removed.

For example, if the value is ‘ and the sample ID in the file</td></tr>
</table>

Item	Meaning
	'ABC123', then the value used to identify the patient record is ABC123.
Ignore string	If a sample ID or result in the file contains the specified string, it is removed. For example, if the value is "ID" and the sample ID in the file is "IDABC123", then the value used to identify the patient record is ABC123.
Qualifying string	Only lines in the file that contain the qualifying string are include when importing data.
Fixed width sample ID start column	If zero, the file is not fixed width. Otherwise, the column number in the line where the sample ID starts.
Fixed width sample ID end column	If zero, the file is not fixed width. Otherwise, the column number in the line where the sample ID ends.
Fixed width result start column	If zero, the file is not fixed width. Otherwise, the column number in the line where the result starts.
Fixed width result end column	If zero, the file is not fixed width. Otherwise, the column number in the line where the result ends.
Database sample ID sub string start	**αlpha** database sample ID start character for matching sample ID read from file. If zero, the whole **αlpha** database sample ID is used for matching. Sample IDs from the file are matched with sample IDs in the **αlpha** database. If a substring of the **αlpha** database sample ID is to be used for matching a non-zero value is specified here.
Database sample ID sub string end	**αlpha** database sample ID end character for matching sample ID read from file. If zero, the whole **αlpha** database sample ID is used for matching.
Data entry field for sample number	The field in the data entry screen used to match the sample ID read from the file. The choices are the data entry screen fields with prompts "Lab number", "ID Code", "Spare 1", "Spare 2","Spare 3", "Spare 4", "Spare 5" and "Spare 6". These fields may have been renamed by the user. **Note:** If the Integrated test is being used, analyte values for second trimester markers are being imported and no matching sample ID is found using the field specified here then the "Lab number" field will also be tested for a matching value. This allows laboratories which perform both integrated and second trimester screening to use the analyser import.
Round assay value	Number of decimal places to which the result should be rounded before being stored in the patient record.
Enter assay date	If "Yes" is selected, today's date is entered as the assay date for this marker.

3.4.2 Example

An import file (which has no header lines) contains the following data in each line:

Sample ID, inhibin-A, AFP, uE3, hCG

An example of a line in the file is:

```
08-7585Z,59.4,21,1.36,4271000
```

The import file configuration would be as follows:

Item	Inhibin-A	AFP	uE3	hCG
File path and mask	Specify full path and location of file			
Header lines in file	0	0	0	0
Field number for sample ID	1	1	1	1
Field number for result	2	3	4	5
ASCII code for field separator	44	44	44	44
Decimal separator	46	46	46	46
Result scaling factor	1	1	1	1
Lower assay limit	0	0	0	0
Quotation character	Leave blank	Leave blank	Leave blank	Leave blank
Ignore string	Leave blank	Leave blank	Leave blank	Leave blank
Qualifying string	Leave blank	Leave blank	Leave blank	Leave blank
Fixed width sample ID start column	0	0	0	0
Fixed width sample ID end column	0	0	0	0
Fixed width result start column	0	0	0	0
Fixed width result end column	0	0	0	0
Database sample ID sub string start	0	0	0	0
Database sample ID sub string end	0	0	0	0
Data entry field for sample number	Select data field required			
Round assay value	Select as required			
Enter assay date	Select as required			

3.4.3 Test import file

The file format specification can be tested by highlighting a marker row and the pressing the Test button on the Analyser Import screen (Figure 30). The Next Next and Previous Previous button can be used to review the whole file to confirm that the sample ID and analyte result are identified correctly. Each line of the file is displayed and the sample ID and result shown in red.

Figure 30: Testing the analyser Import file

3.5 Data transfer settings

With **Data transfer settings** (Figure 31) you can select fields from the MS or AF database which are to be exported to another software program, such as a database or spreadsheet, for further analysis. *Appendix* G *Import, Export, Data transfer and Analyze-it formats* gives the meaning and format of the fields exported using Data Transfer. Once selected here, the chosen fields are exported using the **Statistics** function **Data Transfer** (See Section 5.3).

The fields you select can be saved as a "data transfer specification". If you use data transfer regularly (for example, to export weekly statistics) you only need to specify the fields once; on subsequent occasions you simply select the saved specification.

The following data transfer file formats are available:

- Comma separated (with or without field names)
- Tab separated (with or without field names)

In the comma-separated formats, a comma character appears between the data fields in the export file. In the tab-separated formats, a tab character appears between the data fields in the export file. If you select the option **Include Field name header**, the first row of the export file contains the names of the fields in the order they appear in the file, separated by either commas or tabs, according to the format you selected. The supported formats are compatible with a wide range of statistics, database and spreadsheet software. Please consult the manual for your software if you are not sure which format to use.

You can also select the categories of record you want to exclude from the exported data. You can export all records (rows) in the database, or you can restrict the exported rows by excluding:

- deleted and incorrect reports
- women with insulin-dependent diabetes mellitus
- multiple pregnancies
- updated results and repeat tests

The filename and path for the exported data can also be specified.

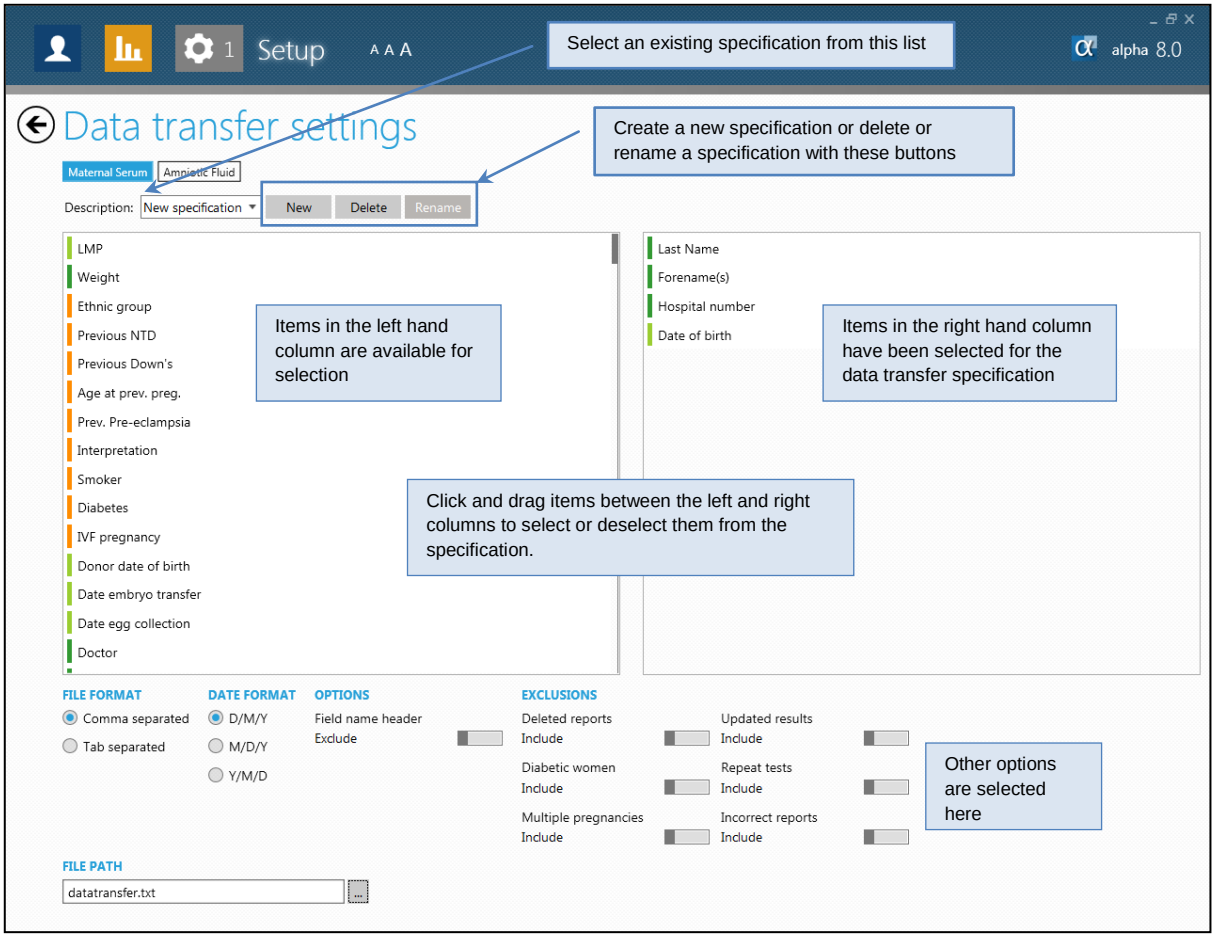


Figure 31: Data transfer settings

3.6 Database

Database provides a facility for making a copy of the αlpha database to another location (see Figure 32). It also provides details about the SQL server database name, SQL server version being used and the location of the database files on the computer running SQL server and their size.

Important: You can only use this facility to copy a database to another location when αlpha and SQL server are running on the same computer. This facility will normally be used when you want to move the αlpha software and database to another computer. In a multiuser configuration please contact your network administrator if you wish to move the αlpha software and database.

To copy the database to another location, browse to the path where you want to copy the database files to (for example a memory stick or another drive), provide a filename and press the “Copy” button. αlpha will copy two files, the SQL server database file (with an MDF extension) and SQL server log file (with an LDF extension) to the specified location. Section 2.11.1 provides details of how to use this facility to move your copy of αlpha to another computer.

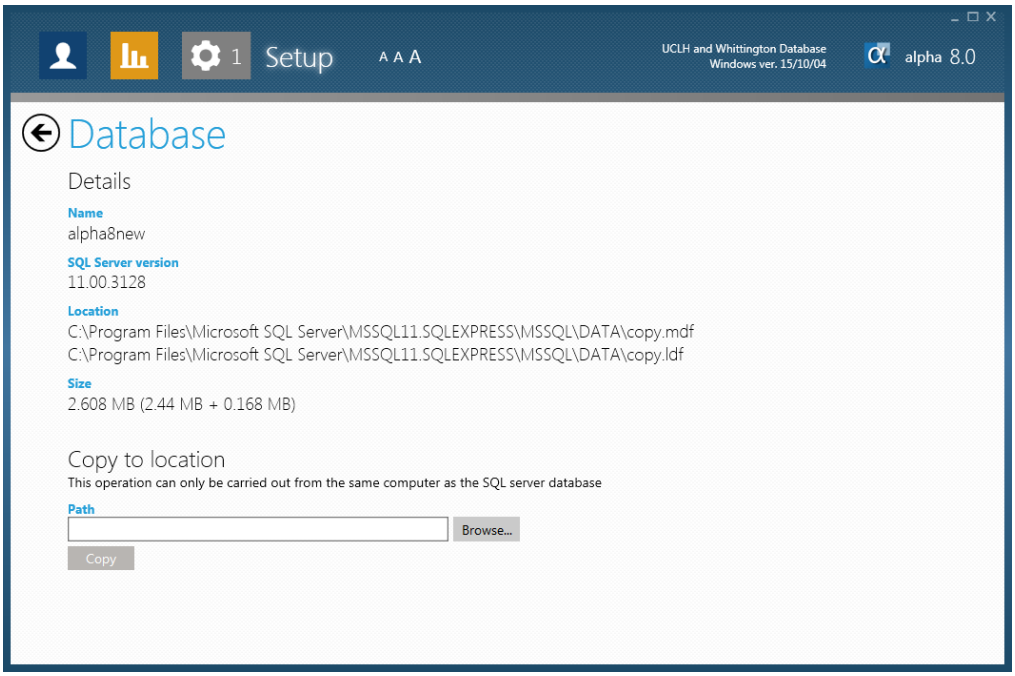


Figure 32: Database

3.7 Doctor codes

Doctor codes provide a way of recording the names of doctors associated with reports using a code to represent each doctor's name. A similar facility is provided for recording the report addresses (Section 3.3 Address codes) and names of sonographers (Section 3.18 Sonographer codes). Using codes reduces data entry time and helps reduce errors. The codes used may be up to eight characters long.

The **Doctors** screen (Figure 33) provides facilities for viewing, editing and deleting stored doctors and adding new doctors. A new doctor can be created with the **New** button and an existing entry modified with the **Edit** button. When these options are selected a window similar to the in Figure 34 is shown which shows all the information which can be stored with the doctor code:

- The report will be shown in the **Language** specified for the doctor. This setting overrides the language selected by the user. (See section 3.21)
- The **First Copy** and **Second Copy** are the Doctor codes which are automatically selected when the Doctor is specified in the data entry screen prompt **Reports To**. (See *Appendix* B *Prompts and their meanings).*
- The **Preferred Addresses** are the addresses which are shown for this Doctor when the button is selected in the Data Entry screen (See section 4.1). The first **Preferred Address** is automatically used as the address when the Doctor is specified in data entry screen prompt **Reports To**. (See *Appendix* B *Prompts and their meanings).*
- The **Exclude** setting will exclude the doctor's name from being displayed elsewhere in **αlpha**. This prevents lists of doctors shown in **αlpha** becoming unnecessarily long.

Use the **Mailshot lists** option to create a text file of doctors' names and addresses, suitable for generating mail shot letters, labels or envelopes. Only doctors who are linked to one or more address codes are included in the mail shot file. You can choose to include all linked addresses for each doctor, or the first linked address only. The text file contains the doctor's full name, and the four lines of the doctor's address, separated by tab characters. The first record in the file contains the field names (*Doctor, Address 1, Address 2, Address 3, Address 4*), also separated by tab characters.

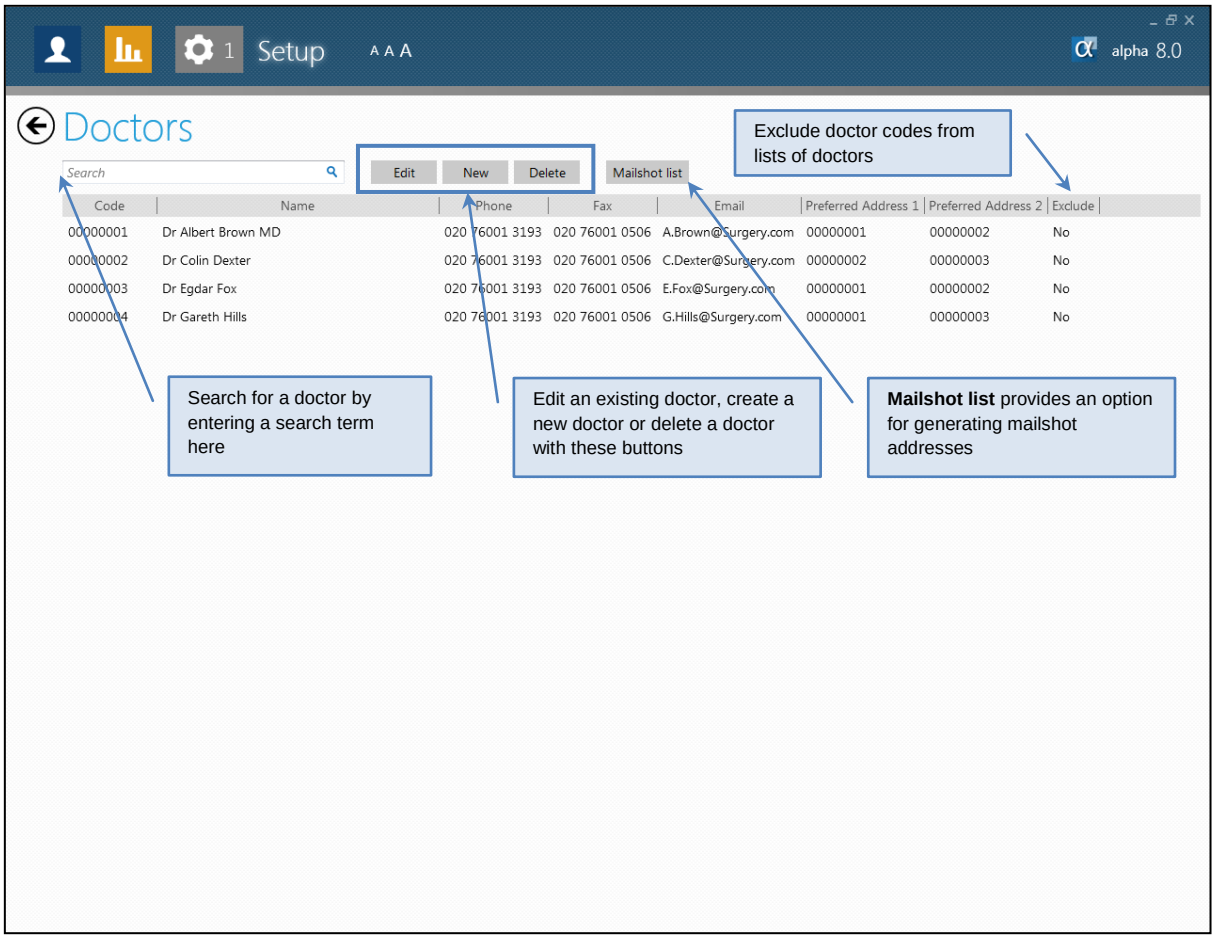


Figure 33: Doctors screen

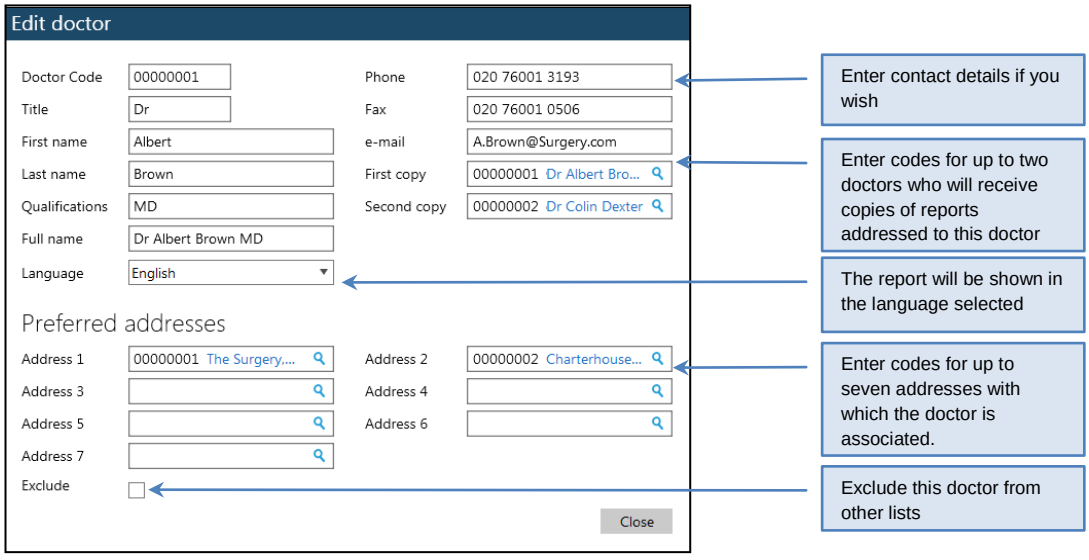


Figure 34: Edit a doctor

3.8 Ethnic groups

With this option you can specify the names **αlpha** uses to refer to different ethnic groups. You can specify a short name and a long name for each ethnic group. The long name (up to 30 characters in length) is printed on **αlpha** reports, and the short name (up to 10 characters in length) is used in menus and statistical summaries.

By default, three ethnic groups are defined in **αlpha** (overall, non-black and black). You can change the names used to refer to these three groups, as well as defining up to three additional ethnic groups of your choice. For each ethnic group defined, you can specify separate ethnic group-specific median equations, weight correction equations, anencephaly prevalences and spina bifida prevalences.

Please note that the group named by default 'overall' and 'black' are reserved for women whose ethnic group is not specified, and for black women, respectively.

3.9 Export settings

If you have created an MS or AF export data format, then each time you create a final report (Section 4.2.3), or a corrected or updated report (Section 4.4), **αlpha** will write selected information from the report to a text file. By default, the text file is called EXPORTMS.DAT for MS reports and EXPORTAF.DAT for AF reports. You can specify your own names for these files if you wish. New information is added to the end of the files if they exist; new files are created if they do not exist.

To create the import data format, highlight the fields in the left hand column of the **Export Settings** screen (Figure 35) that you want to appear in the export file and drag it to the right hand column. To remove a field, highlight it in the right hand column and drag it to the left hand column.

Select the export file format (fixed length, comma-separated, or tab-separated), the date format (d/m/y, m/d/y or y/m/d). If **DOS compatible mode** is selected, the doctor code, address code and sonographer code are taken to be four characters long. If this is not selected, the codes are taken to be eight characters long. Also, if **DOS compatible mode** is selected, NT MoM values in twin pregnancies are exported separated by a "/". If **NT levels to 2dp** is selected, NT levels are exported with 2 numbers after the decimal point. If this is not selected, NT levels are exported with 1 number after the decimal point.

Enter the name for the export file, or leave this field blank to use the default names EXPORTMS.DAT and EXPORTAF.DAT.

Full details of the fields which can be exported are given in *Appendix* G *Import, Export, Data transfer and Analyze-it formats.*

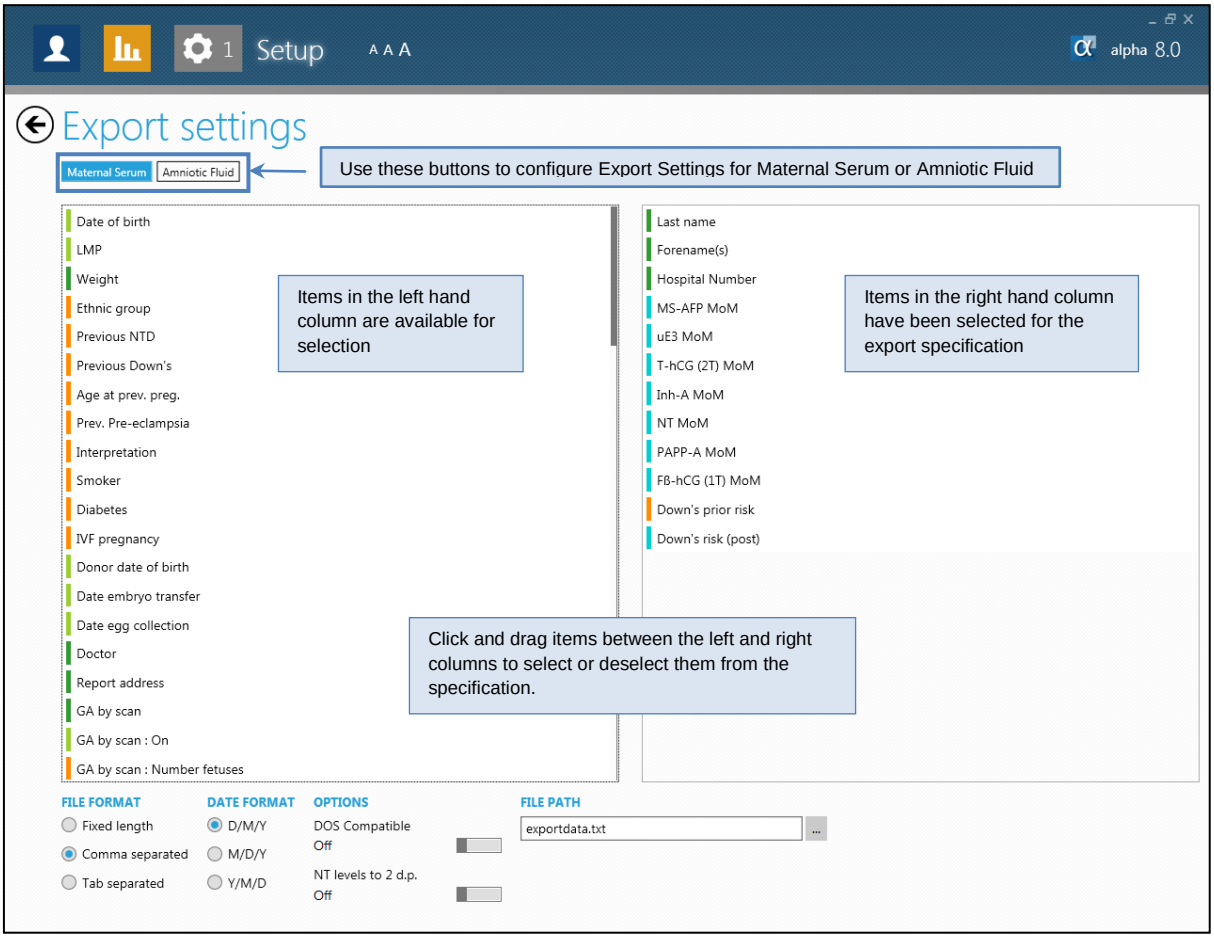


Figure 35: Export settings

3.10 Import settings

Before importing data into **αlpha** from text files, you first need to define the format of the import file. When you select an Import data format option, **αlpha** displays the prompts chosen in **Screen design**. To create the export data format, highlight the fields in the left hand column of the **Import Settings** screen (Figure 36) which appear in the import file and drag them to the right hand column. To remove a field, highlight it in the right hand column and drag it to the left hand column.

Select the import file format (fixed length, comma-separated, or tab-separated), the date format (d/m/y, m/d/y or y/m/d) and the full path and filename of the file containing the data to import.

In fixed length records each field in the record occupies a fixed number of characters, and there are no separators between fields. In addition, dates do not contain separators. In comma-separated and tab-separated records the length of each field is variable, fields are separated with commas or tabs, and dates contain separators.

If **DOS compatible mode** is selected, the doctor code, address code and sonographer code are taken to be four characters long. If this is not selected, the codes are taken to be eight characters long. If **Import NT levels to 2dp** is selected, NT levels are imported with 2 numbers after the decimal point. If this is not selected, NT levels are imported with 1 number after the decimal point.

Full details of the fields which can be exported are given in *Appendix* G *Import, Export, Data transfer and Analyze-it formats.*

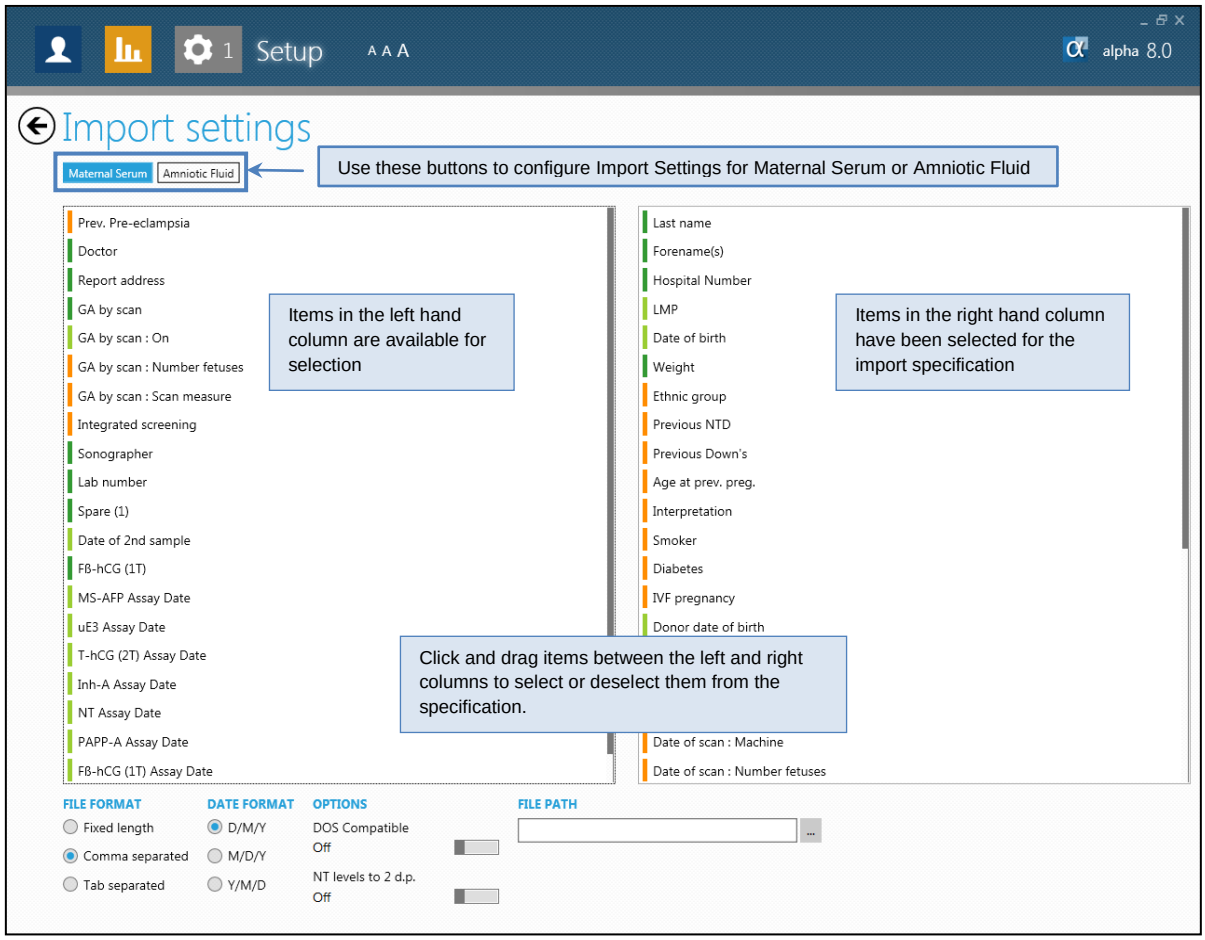


Figure 36: Import settings

3.11 Integrated test options

If you use **αlpha** to interpret Integrated Test results, you may find the Integrated test options useful (See Figure 37). When the Integrated test options are configured, the icons  ,  ,  and  are also shown on the **Patients** screen and can be selected to show lists of patients meeting the criteria specified (See Table 5 and Table 7).

Table 5: Integrated test options

Icon	Title	Description
	Ready to report	An Integrated test is deemed to be ready to report when the markers specified have been measured
	Second sample planner	The ideal gestational age at which the second trimester sample in the Integrated test should be provided
	Reminder list	The gestation age at which patients should be added to the reminder list
	Overdue reminder list	The gestation age at which patients should be added to the overdue reminder list

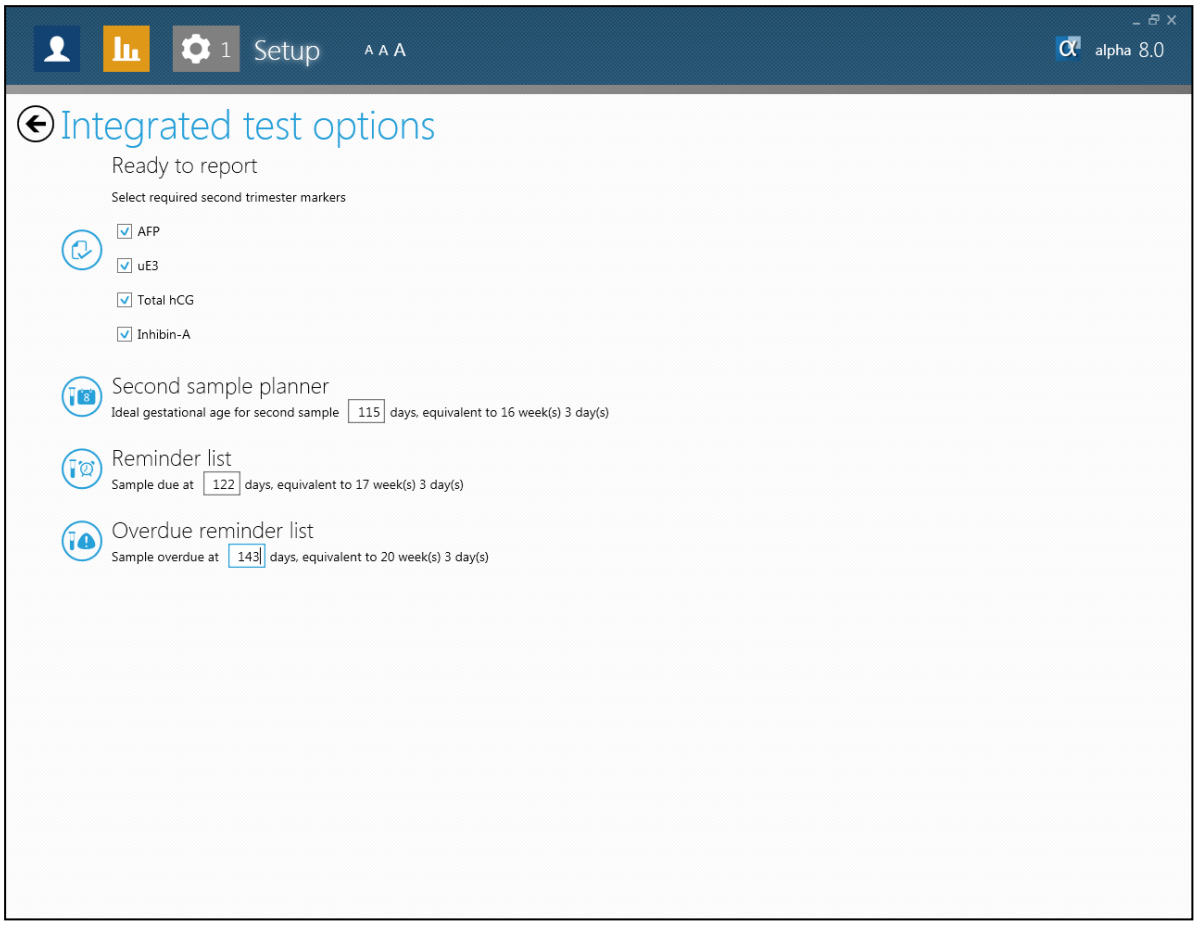


Figure 37: Integrated test options

3.12 Licence

You use this option (Figure 38) to examine the status of your **αlpha** licence, or to renew your licence. The licence status is also shown in the **Setup** screen (Figure 13).

An 'A' credit is used each time you produce a final report for a non-Integrated Test. An 'A' credit and a 'B' credit are used each time you produce a final report for an Integrated Test. A 'C' credit is used each time you produce a final report in which a pre-eclampsia risk is calculated. The appropriate credits are also charged for repeat tests (see section 4.2.2.1). Updates, corrections, test reports, and reprints do not use credits.

αlpha will notify you when the licence is about to expire with one of the following messages:

αlpha usage is approaching the current licence limit (**αlpha** displays this message when less than 10% of the previous allocation of A credits remains)

The licence to use αlpha is due to expire on <date> (**αlpha** displays this message when the expiry date is within 30 days of the current date)

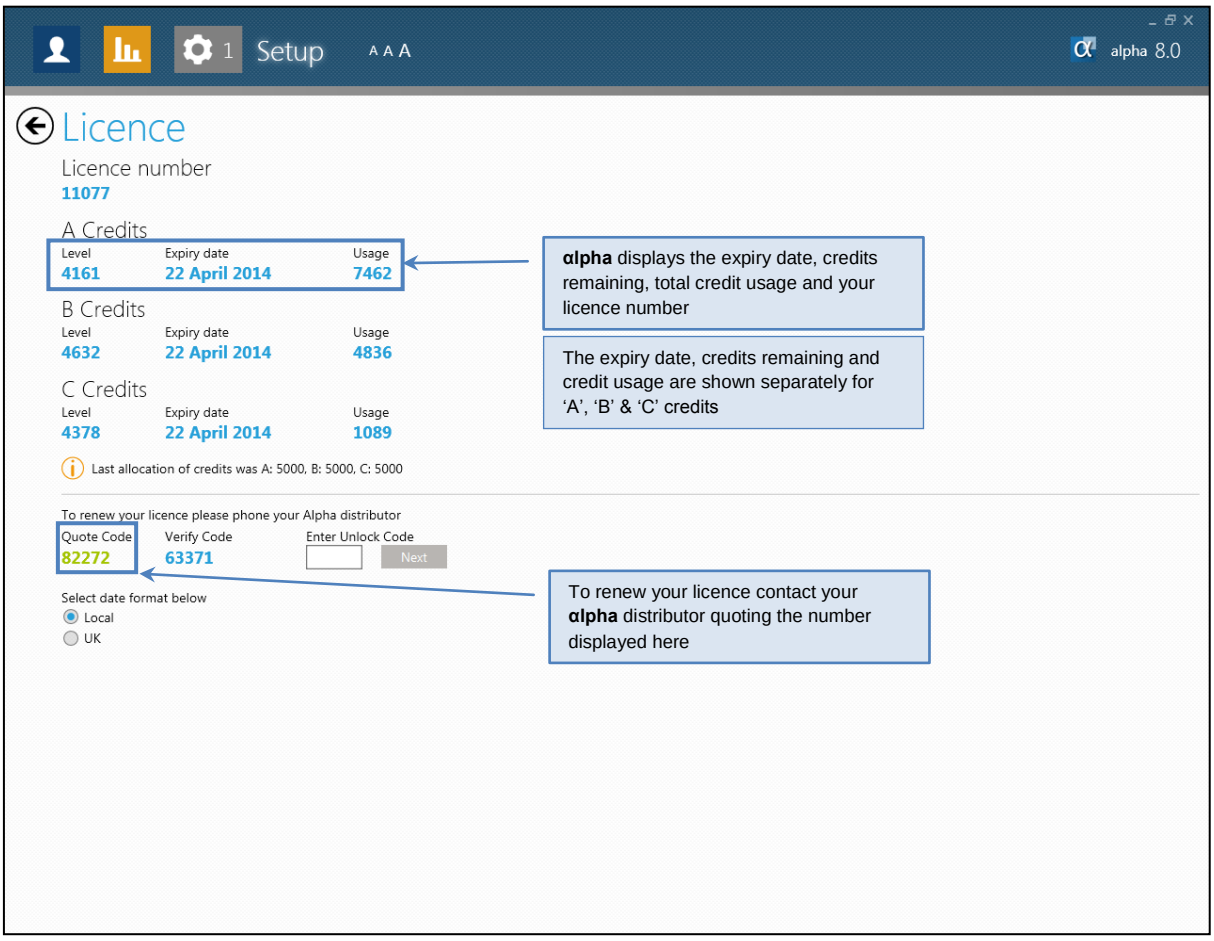


Figure 38: Licence screen

3.13 Markers

The markers section allows you to change the names **αlpha** uses for the screening markers, to review the statistical parameters used for each marker and to add new markers (See Figure 39)

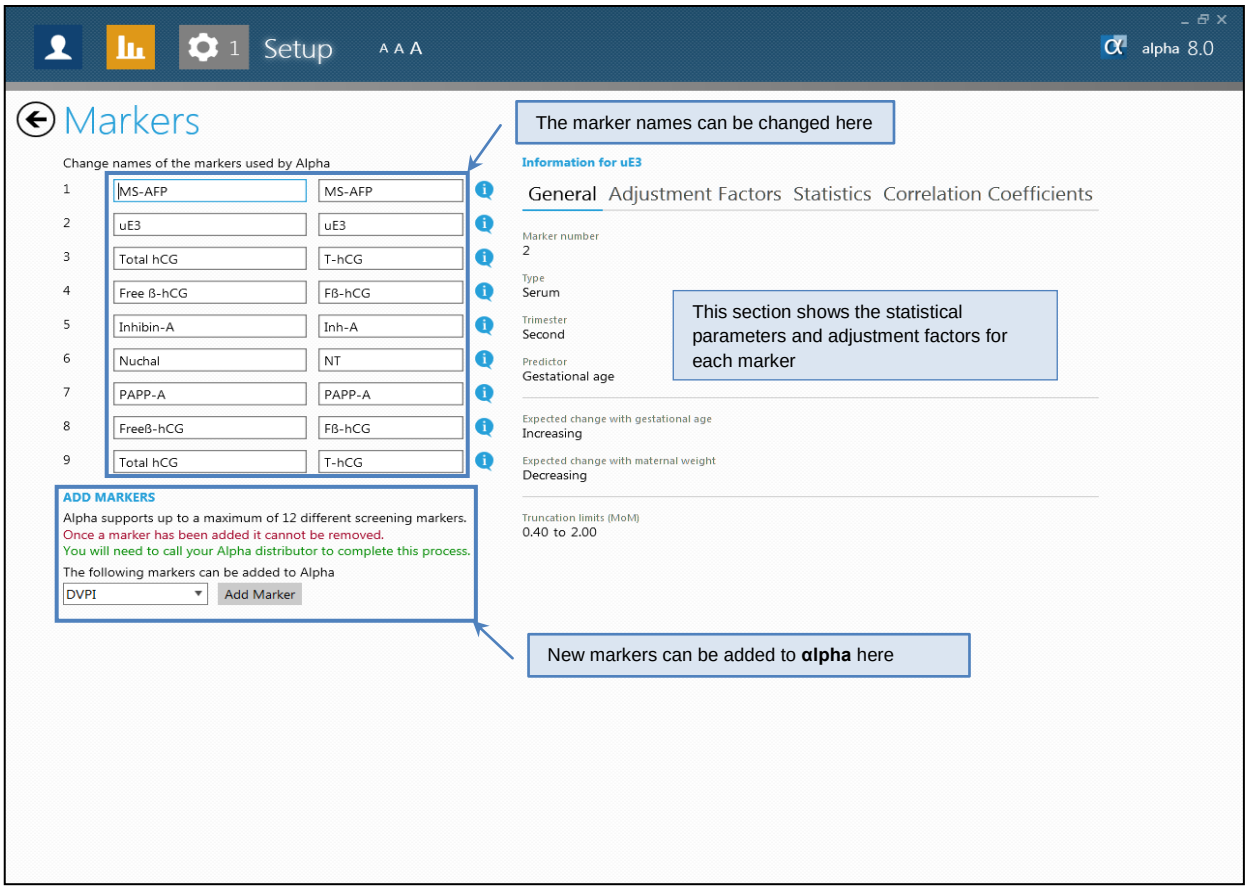


Figure 39: Markers

3.13.1 Changing marker names

With this option you can change the names **αlpha** uses to refer to the installed screening markers. The name of AF-AFP cannot be changed.

You can specify a long name (up to 20 characters in length) and a short name (up to 10 characters in length) for each marker. The long name appears in **αlpha** reports. The short name is used in menus, on the data entry screen, and in statistical summaries.

The identity of a marker does not change when you rename it. For example, **αlpha** will always interpret MS-AFP as the level of alpha-fetoprotein in maternal serum, regardless of any alternative name you give to the marker.

3.13.2 Reviewing marker details

This allows you to review the statistical parameters, adjustments factors and other details associated with each marker. To use this, select the information tab next to the marker.

3.13.2.1 General

3.13.2.1.1 Marker Type

Specifies whether the screening marker is:

- a serum marker
- an ultrasound marker

3.13.2.1.2 Trimester

Specifies whether the screening marker is used in:

- the first trimester of pregnancy (between 10 and 13 weeks)
- the second trimester of pregnancy (between 14 and 22 weeks)

3.13.2.1.3 Predictor for medians

Specifies the predictor variable (i.e. the x-axis variable or independent variable), which is used to derive normal median values of the screening marker. The following predictor variables are used:

- gestational age
- crown-rump length
- none

3.13.2.1.4 Expected change with gestational age

Specifies the direction in which the normal median level of the marker changes with advancing gestation.

3.13.2.1.5 Expected change with maternal weight

Specifies the direction in which the normal median MoM level of the marker changes with increasing maternal weight.

3.13.2.1.6 Truncation limits

Specifies the lower and upper MoM limits (known as the truncation limits) of the range of values for which the distribution of $\log_{10}$ MoM values of the marker is judged to be Gaussian (normal). For the purpose of risk estimation, if a MoM value falls outside this range, the value at the corresponding truncation limit will be used instead.

3.13.2.2 Adjustment factors

3.13.2.2.1 Twin pregnancies

This specifies the median MoM value of the marker in unaffected twin pregnancies. In screening for Down's syndrome in twin pregnancies, MoM values are divided by the corresponding median values in unaffected twin pregnancies, and the risk of Down's syndrome estimated as in singleton pregnancies. This policy will yield a false-positive rate which is, in expectation, similar to that in singleton pregnancies.

Although estimating the risk in this way is a valid way of judging whether a result is positive, it is not the woman's true risk. Neither the true risk nor the corresponding detection rate can be estimated, because the distribution of the serum markers in twin pregnancies with Down's syndrome is not known. (See *Appendix* P *Factors used for adjusting MoM values*)

3.13.2.2.2 Pregnancies in women with insulin dependent diabetes mellitus

This specifies the median MoM value of the marker in unaffected pregnancies in women with insulin-dependent diabetes mellitus. Separate adjustment factors are given according to whether or not the MoM value has been corrected for maternal weight, or not. The use of separate adjustment factors allows for the difference in weight, on average, between diabetic and non-diabetic women.

In screening for Down's syndrome in pregnancies in women with insulin-dependent diabetes mellitus, MoM values are divided by the corresponding median value in unaffected diabetic pregnancies, and the risk of Down's syndrome estimated as in non-diabetic pregnancies. This policy will yield a false-positive rate which is, in expectation, similar to that in non-diabetics. (See *Appendix* P *Factors used for adjusting MoM values*)

3.13.2.2.3 Women who smoke

This specifies the median MoM value of the marker in women who smoke. (See *Appendix* P *Factors used for adjusting MoM values*)

3.13.2.2.4 IVF pregnancies

This specifies the correction factor for adjusting MoM values of the marker in women who have become pregnant through *in-vitro* fertilization (IVF).

In IVF pregnancies, the levels of some serum markers differ, on average, from those in non-IVF pregnancies, and the screen-positive rate may, as a result, be higher or lower than expected. Correcting the MoM values should yield a screen positive rate similar to that seen in non-IVF pregnancies. (See *Appendix* P *Factors used for adjusting MoM values*)

3.13.2.2.5 Recurrent false positive slope

This specifies the slope of the equation relating MoM values in the current pregnancy to a previous pregnancy. This adjustment can reduce the false positive rate by adjusting the MoM values in the current pregnancy for values in a previous pregnancy.

3.13.2.3 Statistics

3.13.2.3.1 Means

This specifies the mean $\log_{10}$ MoM value (usually estimated from the median) for the marker in affected and unaffected pregnancies. For unaffected pregnancies, the expected mean $\log_{10}$ MoM value is 0.0, by definition.
For first trimester markers, this specifies the estimated biochemical marker median and NT median in affected pregnancies with gestational age.

3.13.2.3.2 Standard deviations

This specifies the standard deviations of $\log_{10}$ MoM values of the marker in affected and unaffected pregnancies. Standard deviations are specified separately for gestational age estimated from dates and ultrasound scan, each with and without adjustment for maternal weight.

For NT the standard deviation in unaffected pregnancies at specific gestations is specified.

3.13.2.4 Correlation coefficients

This specifies the coefficients of correlation between $\log_{10}$ MoM values of the marker and other markers in a single maternal serum sample, for affected and unaffected pregnancies. Correlation coefficients are specified separately for gestational age estimated from dates and ultrasound scan, each with and without adjustment for maternal weight.

This also specifies (at specific gestations) the correlation coefficients between $\log_{10}$ MoM values of NT and the biochemical markers in unaffected pregnancies.

3.13.3 Adding new markers

Appendix J *Statistical parameters: Down's syndrome* gives a list of all the markers which can be used with **αlpha**. A maximum of twelve of these markers can be installed for use with **αlpha**.

If you wish to install a marker not currently used in your **αlpha** installation, select the marker in the "ADD MARKERS" section and press the "ADD MARKER". You will need to enter an unlock code provided by your **αlpha** distributor to complete the installation. *Once the marker has been added it cannot be removed from **αlpha**.*

Once the marker has been added you will need to:

- Add the marker to the data entry screen (See Section 3.17 *Screen design*)
- Decide the median equation policy to use (See Section 3.1.8 *Median equation policies*)
- Specify normal median equations and weight regression equations (See Section 3.13.3.1 below)
- Specify the units of measurement (See Section 3.1.13 *Units*)
- Update the import and export formats (if required) (See Section 3.10 *Import settings* and Section 3.9 *Export settings*)

The above process would also be followed if you were to start using a marker which was already installed in **αlpha** but not previously used.

3.13.3.1 Normal median equations (Serum markers)

For new serum markers you will need to provide the coefficients for the equations which are used to calculate the normal median value of the marker at different gestational ages. The number of equations you provide will depend on:

- whether the maternal serum data entry screen includes a prompt for the woman's ethnic group
- the median equation policies you have specified (See Section 3.1.8 *Median equation policies*)

Median equations for the overall population must always be provided. If the maternal serum data entry screen includes a prompt for the woman's ethnic group, you may also provide median equations for women of different ethnic groups.

For each ethnic group, you should provide either a single median equation, or two separate median equations, according to the median equation policy specified.

Normal medians should be established by assaying, in your laboratory, samples drawn between 14 and 22 completed weeks of pregnancy (for second trimester markers) or between 10 and 13 completed weeks (for first trimester markers). A minimum of 50 samples per week in four gestational weeks is recommended.

Group the samples by completed week of gestation. Then, for each group, determine the median gestational age in days, the number of samples, and the median marker level in concentration units, and tabulate the data as in the example Excel spreadsheet shown in Figure 40.

	A	B	C	D	E
1	**Gestational age (completed weeks)**	**Median gestational age (days)**	**Number of samples**	**Median uE3 level (ng/mL)**	
2	14	102.0	27	1.97	
3	15	108.5	144	2.72	
4	16	115.0	258	3.58	
5	17	121.5	124	4.67	
6	18	128.0	62	5.92	
7	19	136.0	37	7.30	
8	20	143.0	22	8.46	
9	21	149.0	11	9.16	
10	22	156.0	3	10.20	
11					

Figure 40: Derivation of normal medians for serum markers

Figure 40 relates to a second trimester marker. For a first trimester marker, you would tabulate the data for weeks 10, 11, 12 and 13.

The tabulated median data may then be entered directly into **αlpha**'s regression facility, which derives the coefficients of the regressed median equation *(See Section 5.9.1).* Provided the fit is sufficiently good, the coefficients derived in the regression may be entered into **αlpha**. (See *Section* 3.2 *Coefficients*)

3.13.3.2 Normal median equations (Ultrasound markers)

For a new ultrasound marker, such as nuchal translucency, you will need to provide the coefficients for the equation which is used to calculate normal median values of the marker at different crown-rump length (CRL) measurements.

Normal median values should be established by measuring the ultrasound marker and the CRL between 10 and 13 weeks in approximately 200 women from the population to be screened. Measurements should preferably be uniformly distributed between CRL bands (at least 50 in each band). Preferably, sonographer-specific normal medians will be established for each sonographer who provides ultrasound marker measurements in your screening programme.

Having collected the measurements, group the data in 10 mm CRL bands. For each group, find the median CRL measurements, the number of women, and the median ultrasound marker measurement. Then tabulate the data as shown in the example Excel spreadsheet shown in Figure 41

	A	B	C	D	E
1	**CRL group (mm)**	**Median CRL (mm)**	**Number of women**	**Median NT measurement (mm)**	
2	<40	38.0	3	1.00	
3	40-	47.0	47	1.15	
4	50-	55.2	142	1.30	
5	60-	64.3	173	1.50	
6	70-	73.9	95	1.70	
7	80-	81.6	22	1.80	
8	>=90	90.0	1	1.70	
9					

Figure 41: Derivation of normal medians for nuchal translucency

The tabulated median data may then be entered directly into **αlpha**'s regression facility, which derives the coefficients of the regressed median equation *(See section 5.9.1).* Provided the fit is sufficiently good, the coefficients derived in the regression may be entered into **αlpha** (See *Section* 3.2 *Coefficients*)

3.13.3.3 Weight adjustment equations

If your maternal serum data entry screen includes a prompt for the maternal weight, you will need to provide coefficients for the equations **αlpha** will use to adjust MoM values of the new marker for maternal weight.

To derive the coefficients, create a table consisting of maternal weight bands of 5 kilograms or 10 pounds. Within each weight band, record the median maternal weight, the number of samples, and the median marker level in MoM before adjustment for maternal weight.

The unadjusted MoM value for each sample is derived by dividing the observed marker level in concentration units by the expected marker level given the woman's gestational age. The expected marker level is in turn derived from the median equation for the marker and the gestational age.

Consider the following example:-

Gestational age (GA): 15 weeks, 3 days (108 days)
AFP level: 32.6 iu/mL
AFP median equation:

$$Expected\ AFP\ level = A \times B^{GA\ (days)}$$

where A = 2.674144 and B = 1.020815

The expected AFP level is $2.674144 \times 1.020815^{108} = 24.7\ iu/mL$. The AFP MoM value (before adjusting for maternal weight) is simply the observed AFP level divided by the expected level, that is, 32.6/24.7 or 1.32 MoM. Repeat this calculation for each sample, and summarise the data as described above. You can use a spreadsheet or other software to automate this calculation.

Having summarised the data, enter the values from the table into **αlpha**'s regression section to obtain the coefficients (*See Section 5.9.2*).

If weight adjustment data are not available for the new marker, you can enter coefficients that will allow you to collect weight data without adjusting for maternal weight. The values to use will depend on whether you specify the log-linear model or the linear-reciprocal model for adjusting the marker for maternal weight *(see Section 3.2.3)*. For the log-linear model, enter the value 1.0 for both coefficient A and coefficient B. For the linear-reciprocal model, enter the value 1.0 for coefficient A and the value 0.0 for coefficient B. Once sufficient data have been collected, you can use the **Tabulation** option in **αlpha** to derive the appropriate weight adjustment coefficients.

3.14 Message addition

Message addition allows you to add your own locally-defined messages depending on the screening or diagnostic result. The messages are defined in the **Message Addition** screen (Figure 42).

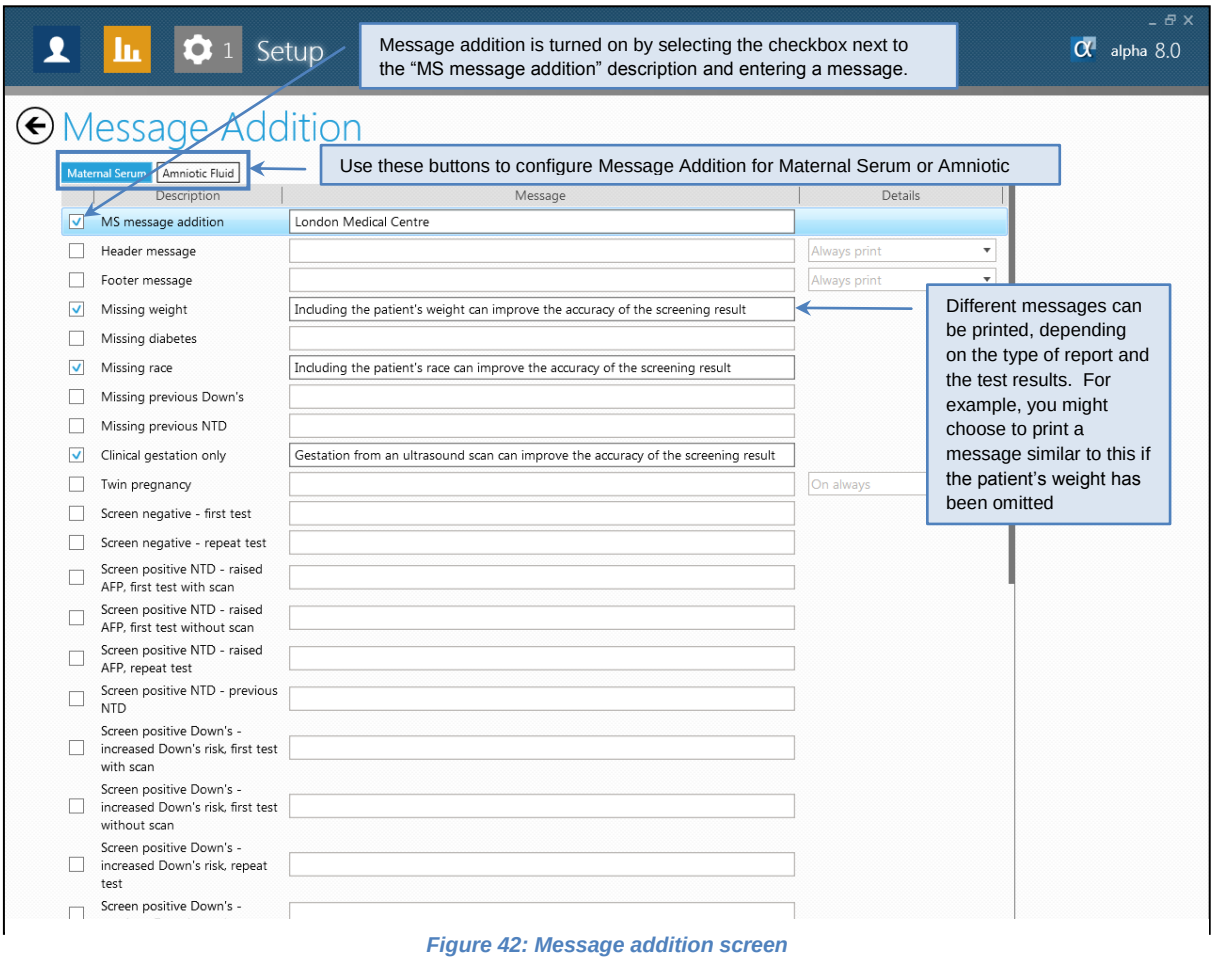


Figure 42: Message addition screen

The **Message addition** screen displays each of the categories of message in the left-hand column. A check box next to each category indicates whether it is currently on or off. Enable messages for a particular category by selecting the check box and then enter or edit the text of the message in the middle column. In some categories you can choose to print only under certain circumstances. For example, for the header message, you can choose to print the message always, or to print it only if other messages appear.

Appendix E *Message addition categories* lists each of the report categories which can generate a message for maternal serum reports.

3.15 Page setup

You use **Page setup** (Figure 43) to specify up to four **Print Styles** (A, B, C and D) that you can associate with the various types of printed output produced by **αlpha** (for example, patient reports, statistical tabulations, listings and error reports). A **Print Style** controls the paper size, margins, and line spacing used for each type of printed output.

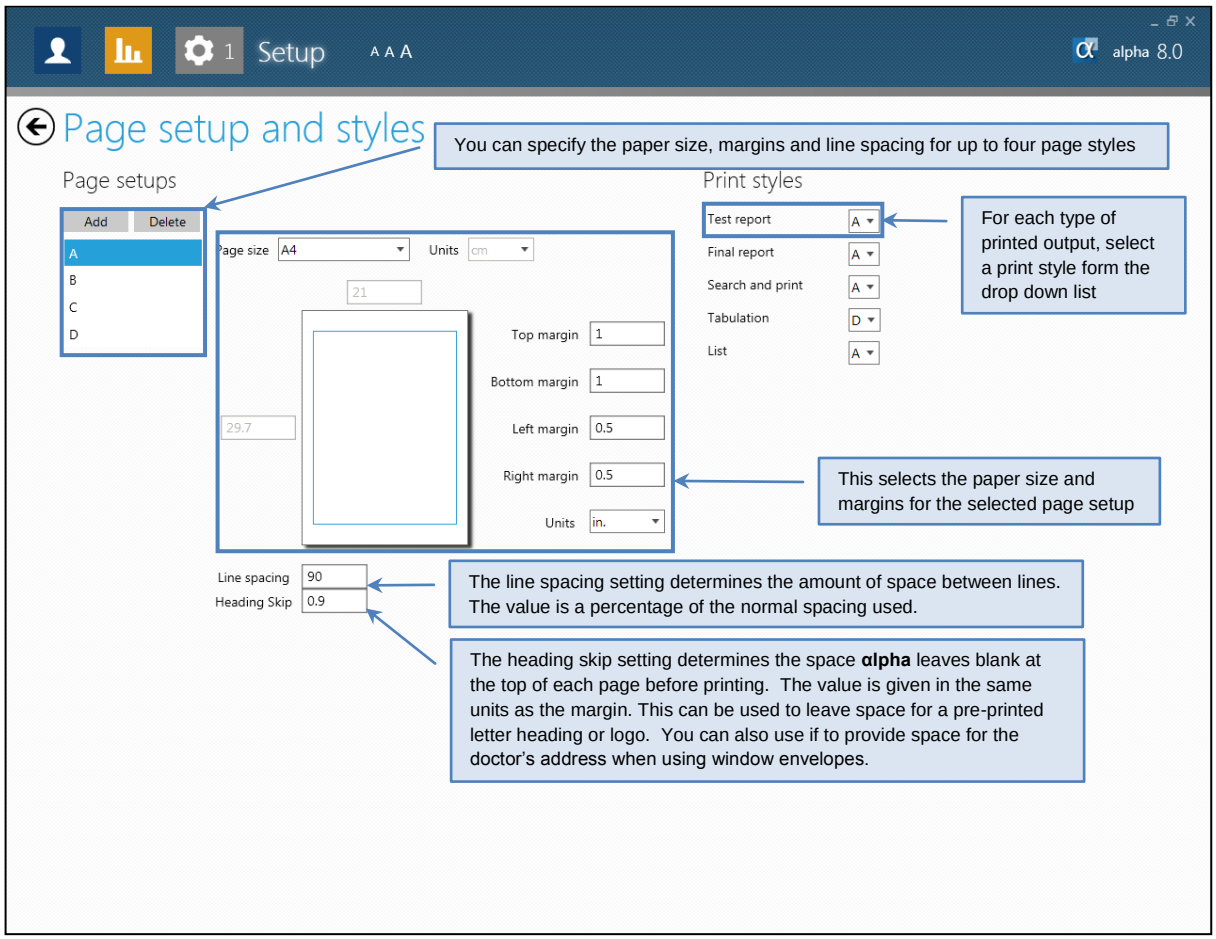


Figure 43: Page setup

The **Report format** option (Figure 44) allows you to choose the report definition files (**RDF**) to use for **MS** and **AF** reports.

An RDF contains a description of the report layout (for example, the position, size and font for each item in the report). **αlpha** is supplied with a standard **RDF** (**ALPHA8.RDF**) which is designed to produce standard format **αlpha** reports on any printer, on the screen, or in export files.

The report layout can be modified by installing an alternative **RDF**. To install an **RDF**, type the name of the file in the appropriate position in the **Report formats** screen. Click on a browse button ... to locate an RDF using the standard file browser window. Click **OK** to save your changes.

Please contact your **αlpha** distributor for information on obtaining customised RDFs.

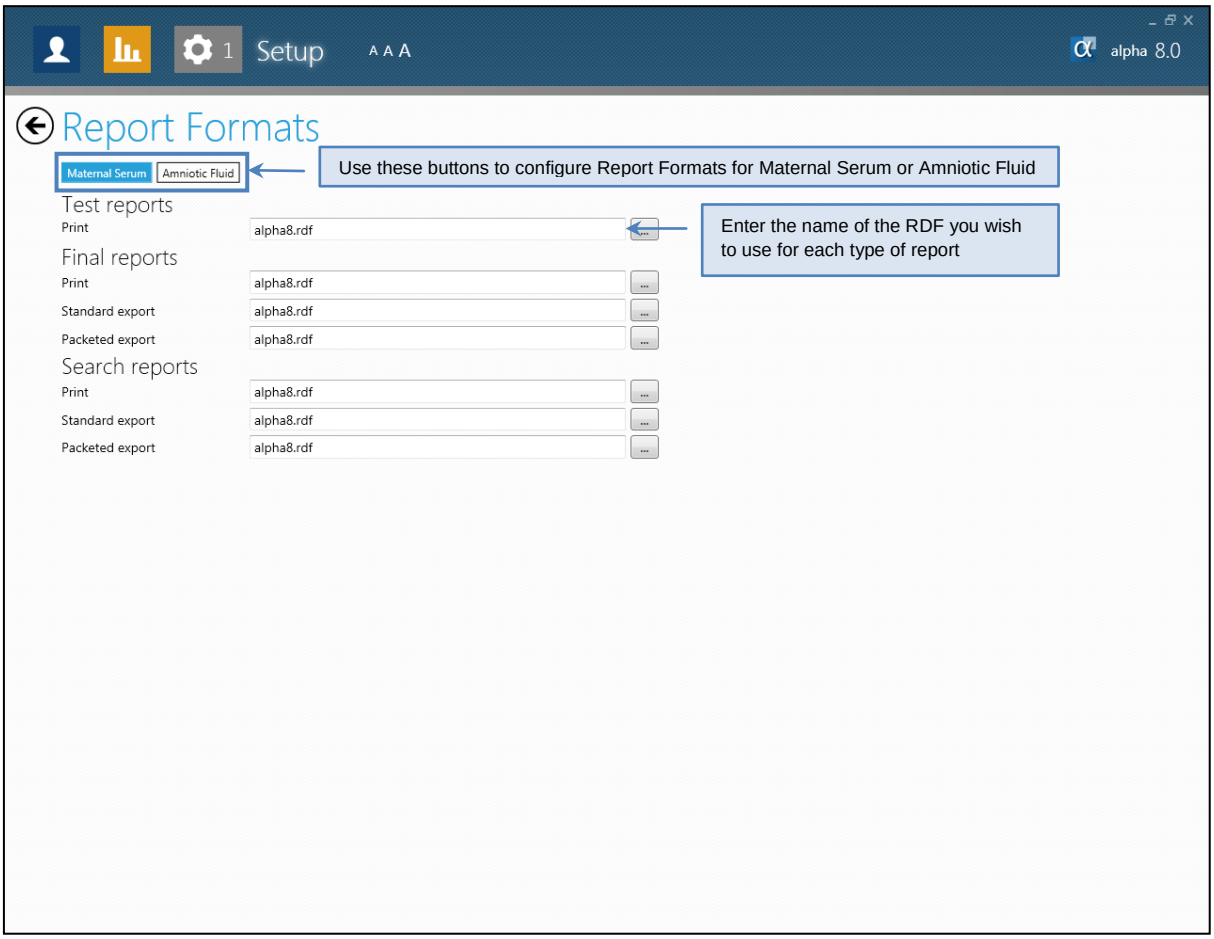


Figure 44: Report Format Settings

3.17 Screen design

You can choose which prompts appear on the data entry screens, and specify the layout on the screen. A separate set of prompts is chosen for maternal serum and amniotic fluid tests. The prompts and blank lines can be arranged in up to five columns.

The MS screen design screen is shown in Figure 45. The left hand column lists all of the fields you can use in the MS data entry screen and the columns on the right show the fields that have been added to the screen design. You add and remove fields by clicking and dragging the items between these columns.

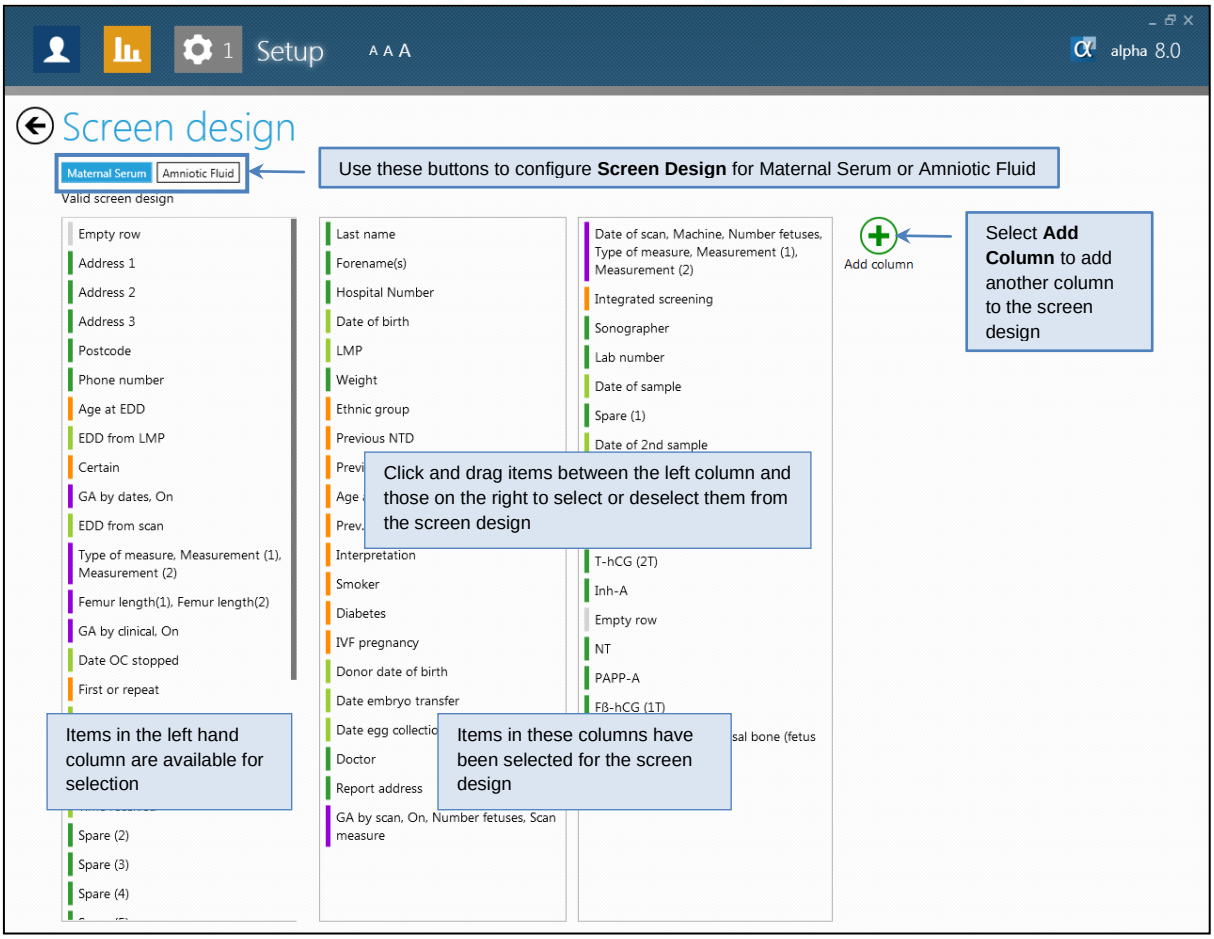


Figure 45: Screen Design

You will find data entry is easier if the order of the prompts on the screen is the same as the order on the screening requisition form. *Appendix* B *Prompts and their meanings* shows the complete set of possible prompts.

You can choose your own names for the prompts by double clicking on a selected prompt. The **Field information** screen is shown where you can enter an alternative name for the prompt (Figure 46). You can give a prompt any name up to 50 characters long. The meaning of the prompts does not change when you rename them. For example, **αlpha** will continue to interpret data entered in the *Date of sample* prompt as the date on which the blood or amniotic fluid sample was taken, regardless of any alternative name you may give the prompt.

If you wish, **αlpha** can automatically complete specified fields in the data entry screen as you move the cursor over them, to save unnecessary repetitive data entry. For example, you could have **αlpha** automatically complete the *Ethnic group* field with the code corresponding to the majority ethnic group. The value entered automatically can be overridden if necessary. Different default values can be used for maternal serum and amniotic fluid AFP screening if required. The default values are also entered in the **field information** screen (See Figure 47)

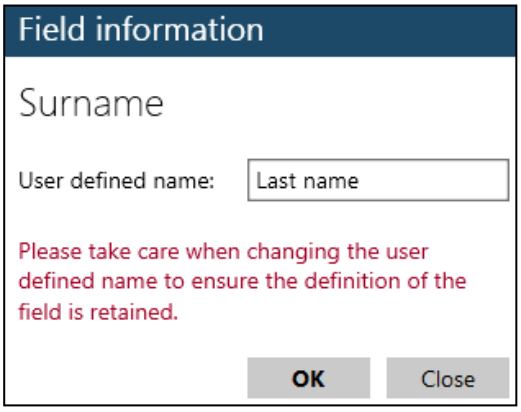


Figure 46: Screen Design - change prompt

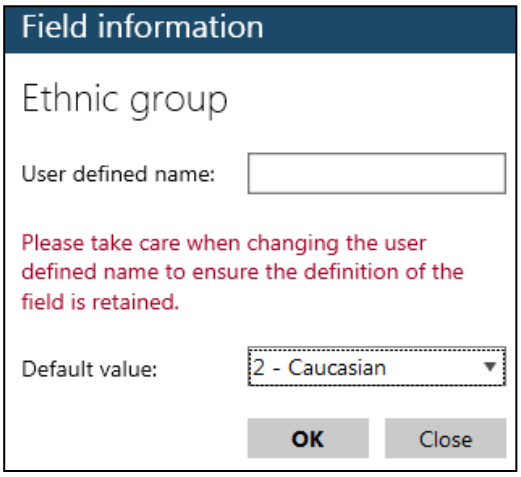


Figure 47: Screen Design - enter default value

αlpha will confirm when the screen design you have entered is valid. Your screen designs must include the following prompts:

- **Surname** or **ID Code**
- **Date of Birth** or **Age at EDD** (only required for MS data entry screen)
- At least one estimate of gestational age (GA)
- **Date of Sample**
- At least one maternal serum or ultrasound marker or **AF-AFP**

Data entered using the prompts are used by **αlpha** for the interpretation or for other purposes. All input data are stored in the database. The spare fields, Spare(1) – (6), are not used in the interpretation, but you can choose whether they are printed on the reports; if they are printed, they appear immediately above the **CLINICAL DETAILS** section of the report.

The screen may be redesigned at any time. However, the format of the reports, including reprinted reports, will always be governed by the current screen design.

3.18 Sonographer codes

Sonographer codes provide a way of recording the names of sonographers associated with reports using a code to represent each sonographer's name. A similar facility is provided for recording the names of doctors (Section 3.7 Doctor codes) and addresses (Section 3.3 Address codes). Using codes reduces data entry time and helps reduce errors. The codes used may be up to eight characters long. Further information of the use of sonographer codes is given in Sections 5.6 and 6.3.2.

3.19 Titles and signature messages

The **Titles** option allows you to add, change or remove the screen and report title.

(i) Screen title

The **screen title** is displayed when you start **αlpha**. You can enter up to two lines of 80 characters. Edit the text as required. To remove the screen title, delete the text.

(ii) Report title

The **report title** is printed at the top of each final report. You can enter up to four lines of 80 characters. Edit the text as required. To remove the report title, delete the text. Extra blank lines after the report title are not printed on the report.

You can specify a **Signature message** of up to 80 characters to be printed at the end of all reports. The signature message consists of the words 'Reviewed by' (or the equivalent in the selected report language) followed by your own message. You can also specify the position of the signature message, relative to the left margin of the page, by entering an offset, between 0 and 50 characters.

3.20 User options

αlpha provides a variety of options for data entry and reporting. These are accessed from **User options** (Figure 48) and are described below:

3.20.1 General

Hide all AF options: Use this option to hide menu options that relate to amniotic fluid (AF) tests. You can show the AF menu options by selecting this option again. If you never use the facilities provided by **αlpha** for interpreting AF tests, you may prefer to hide them

GA Format: Selects comma (,) or plus (+) as the separation character between weeks and days when **αlpha** prints or displays a gestational age (GA). For example, a gestational age of 15 weeks and 4 days would appear as **15,4** or **15+4**, depending on the setting you choose.

Save patient data in data entry: This setting controls how patient data is saved when moving between patients in the data entry screen. When **Manual** is selected **αlpha** will prompt the user to confirm that the data should be saved. When **Automatic** is selected, **αlpha** will automatically save the data.

3.20.2 Print Order

Group Screening Results: Group final reports together which are positive, uninterpretable and negative

Additionally order by: Within the grouped categories above, final reports can also be ordered by Date entered, Surname, ID Code, Patient's address, Doctor, report address or Date of birth.

Print αlpha logo on reports: Specify whether the **αlpha** logo  and the message *This is an **αlpha** report* appear on screening and diagnostic reports

3.20.3 Report export format selection

These options select whether reports should be available for export in standard and/or packet format (See Section 4.2.3).

3.20.4 Auto complete

If you prefer, **αlpha** can automatically complete the woman's name, address, post code, phone number, date of birth and ethnic group, based on the ID code you type in the data entry screen, if a woman with the same ID code is found in the database. This option may be helpful in settings where the *ID code* field is used to record a permanent patient-specific code, such as a Health Service number.

Additionally, **αlpha** can automatically complete the first and second date of sample and the first and second sample receipt date and assay dates, based on the last value entered. This helps to avoid unnecessary repetitive data entry in situations where most or all of the samples in a batch tend to be drawn or received on the same day

3.20.5 XPS filename for reporting

Each final reports can be written to a single XPS (XML Paper Specification) file. This option allows the name of the file to be specified and it can be built from a combination of the patient's surname, forenames and ID code and the report date.

3.20.6 Patient Printing

This option determines the appearance of the reports printed using the Print button on the Patients screen (See Section 4.8). Different formats can be specified for Maternal Serum, Amniotic Fluid and the Integrated test list (See Section 3.11). For each case the columns which appear in the list, the column on which they are sorted and column used to group separate sections can be chosen by pressing the button and selecting from the list of fields. The default settings are shown in Table 6.

Table 6: Default settings for Patient Printing

	Fields	Grouping	Sorting
Maternal Serum	Surname, Forename, Date of birth and ID Code	None	None
Amniotic Fluid	Surname, Forename, Date of birth and ID Code	None	None

Integrated test list	Surname, Forename, Date of birth, ID Code, Second sample due date, GA Now and Batchname	None	GA Now

3.20.7 Nuchal Translucency Monitor

The Nuchal Translucency Monitor option is used together with the Analyse Codes feature in Nuchal Translucency Monitor (See section 5.6). It allows a range to be specified for median NT MoM, standard deviation of $\log_{10}$(NT MoM) and rate of increase of NT per week. Sonographers in the list prepared by the Analyse Codes feature who have measurements outside of this range are indicated by the symbol.

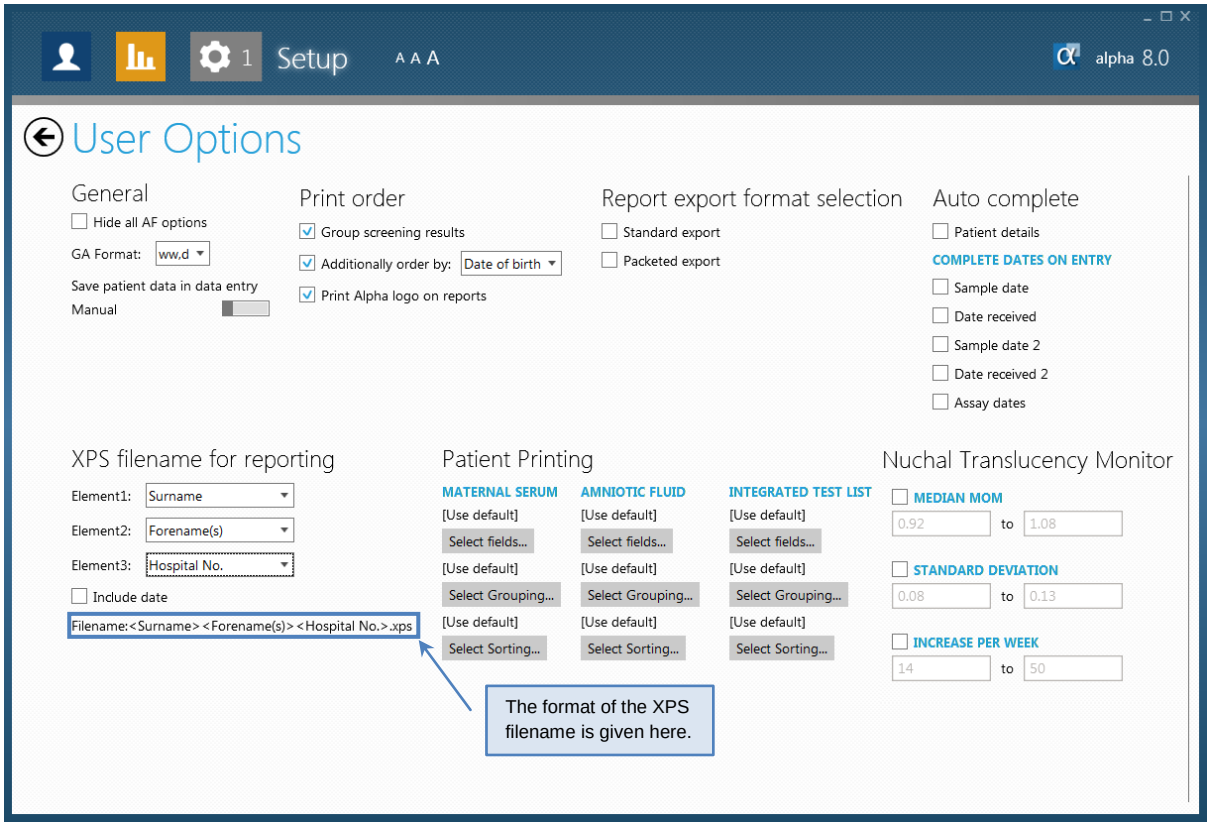


Figure 48: User Options

3.20.8 Error log path

The path used by αlpha to store the error logs is shown here. Your αlpha distributor may ask you to send the error log files to help with the diagnosis of problems. This folder is opened by pressing the "Open folder" button.

3.21 Users

This option allows the system administrator to manage the list of users who can access **αlpha**, by assigning usernames, passwords, password expiry dates, security levels and the language in which the user's data entry screen appears *(See Section 4.1)* and screening reports (Figure 49). When **New User** is selected (Figure 50), the new user's details and security levels can be entered.

αlpha is supplied with one user account, the SYSALPHA or system administrator account. This account has security level 6 and it is the only account which can create, modify or delete other user accounts. *Appendix* F *Controlling access using security levels* gives details of the security levels available.

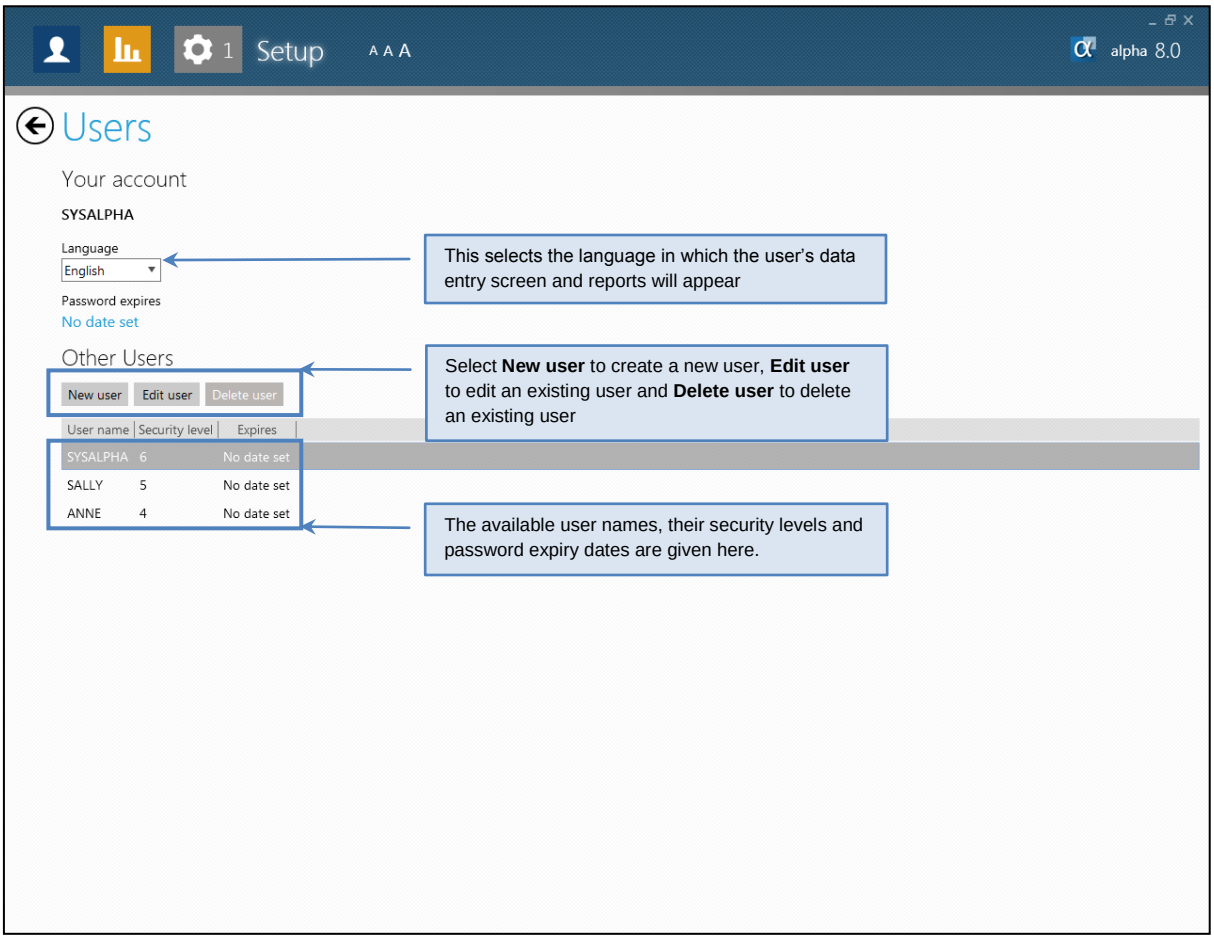


Figure 49: Users

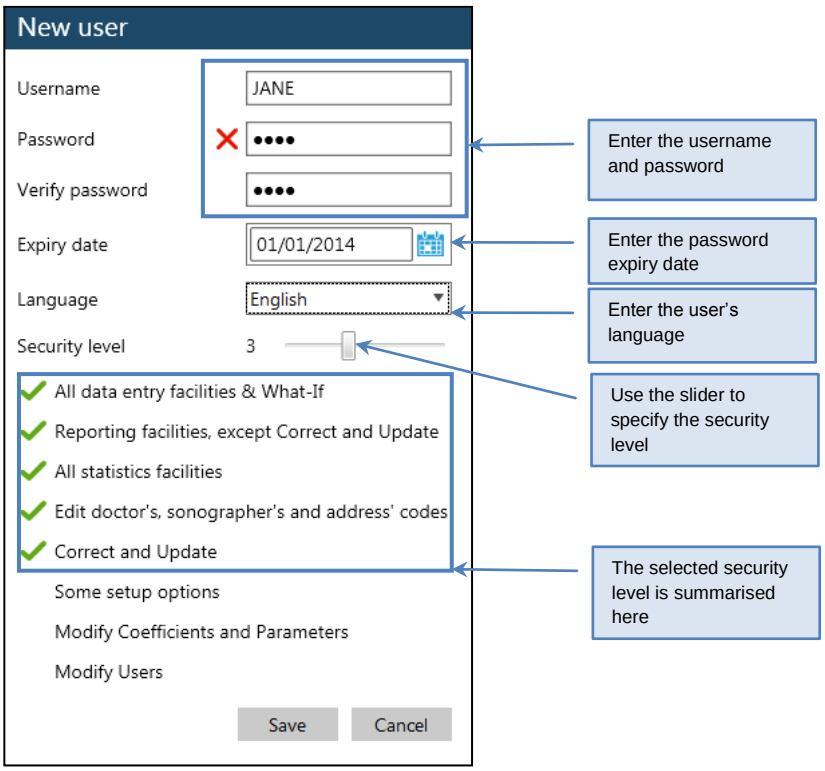


Figure 50: Entering a new user

3.22 What-if

What-if is an educational tool in antenatal screening for open neural tube defects and Down's syndrome. **What-if** can be helpful in understanding how changes in a patient's clinical details and test results, and changes in the screening policy, can affect the interpretation of screening tests. **What-if** provides similar interpretations to those provided by **αlpha**, but the information entered is not stored in the database. **What-If** is not intended for use in a screening service to interpret and report patient results; it should not be used in this way.

When you open **What-if**, **αlpha** displays a screen in which you enter information about the pregnancy, and screening test results (See Figure 51). Provided that sufficient information has been entered (age at EDD, at least one estimate of gestational age, and at least one screening marker level) and that the screening policy settings have been specified (see below), an interpretation is displayed. The interpretation is updated immediately to reflect any changes you make in the pregnancy details, test results or screening policy.

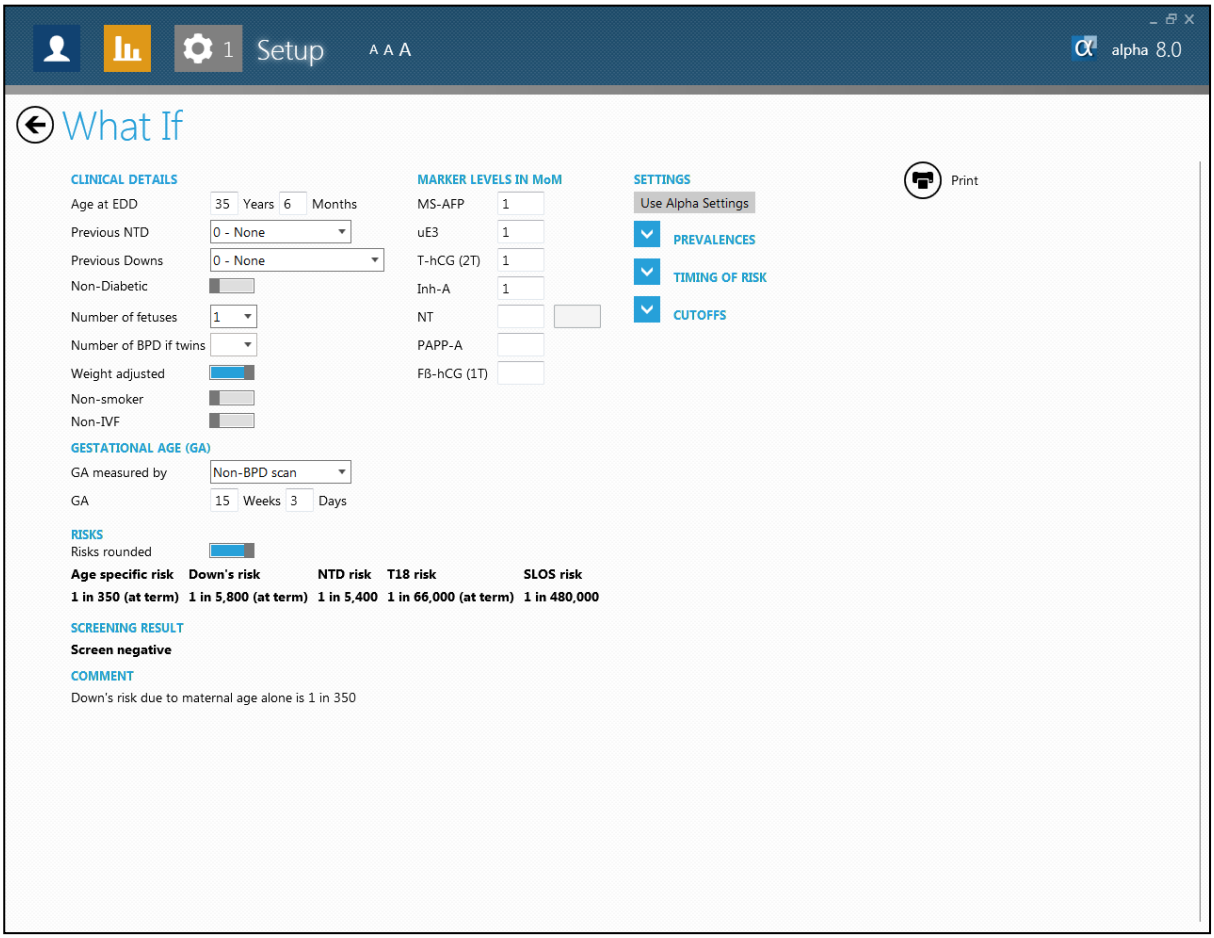


Figure 51: What-if

Open the Prevalences, timing of risk or cutoffs expander to change the settings as required, or you can select the settings used in **αlpha** by clicking **Use αlpha Settings**. Changing the screening policy settings in **What-if** has no effect on the settings used by **αlpha**.

The last screening policy settings used in **What-if** are stored, and are loaded the next time you open **What-if**. So, apart from the first time you use **What-if**, there is no need to specify the settings each time. Of course, you can change the settings at any time to see the effect this has on the interpretation.

What-If provides interpretations for first trimester, second trimester, and integrated screening tests:-

- For first trimester screening tests, enter a gestational age (GA) between 10 and 13 weeks, and enter MoM values for first trimester screening markers only. What-If uses the appropriate gestation-specific parameters in estimating the risk of Down's syndrome.
- For second trimester screening tests, enter a GA between 14 and 22 weeks, and enter MoM values for second trimester screening markers only.

- For integrated screening tests, enter MoM values for first and second trimester screening markers and enter either a first trimester (10-13 weeks) and a second trimester (14-22 weeks) GA. **What-If** uses the appropriate gestation-specific parameters for the first trimester screening markers in estimating the risk of Down's syndrome.

3.23 Window envelope

With this option you can control the position of the doctor's name and report address on the report, in order to use window envelopes when dispatching reports, as shown in Figure 52. The address window can contain up to 10 lines of 30 characters, and may include the doctor and address information, any of the spare fields, blank lines, and a single line of fixed text.

To select fields for the address window, click and drag the field from the left column to the right column. If you select **Add Fixed text**, **αlpha** prompts you to enter the text to use.

To remove a field, click and drag the field from the right column to the left column.

To specify the position of the address window, enter the offsets from the left edge and top edge of the printable area of the page. The offsets can be measured in either cm or inches. The offsets are measured from the position of the left hand margin and top margin and are independent of the **Heading skip** settings (See Section 3.15). It is possible to position the address window so that it overwrites part of the **αlpha** report text. You can avoid this by either of the following methods:

- position the address window in an unused area of the report (for example, to the right of the PATIENT DETAILS section)
- Position the report text below the address window using the **Heading skip** setting in **Page setup**.

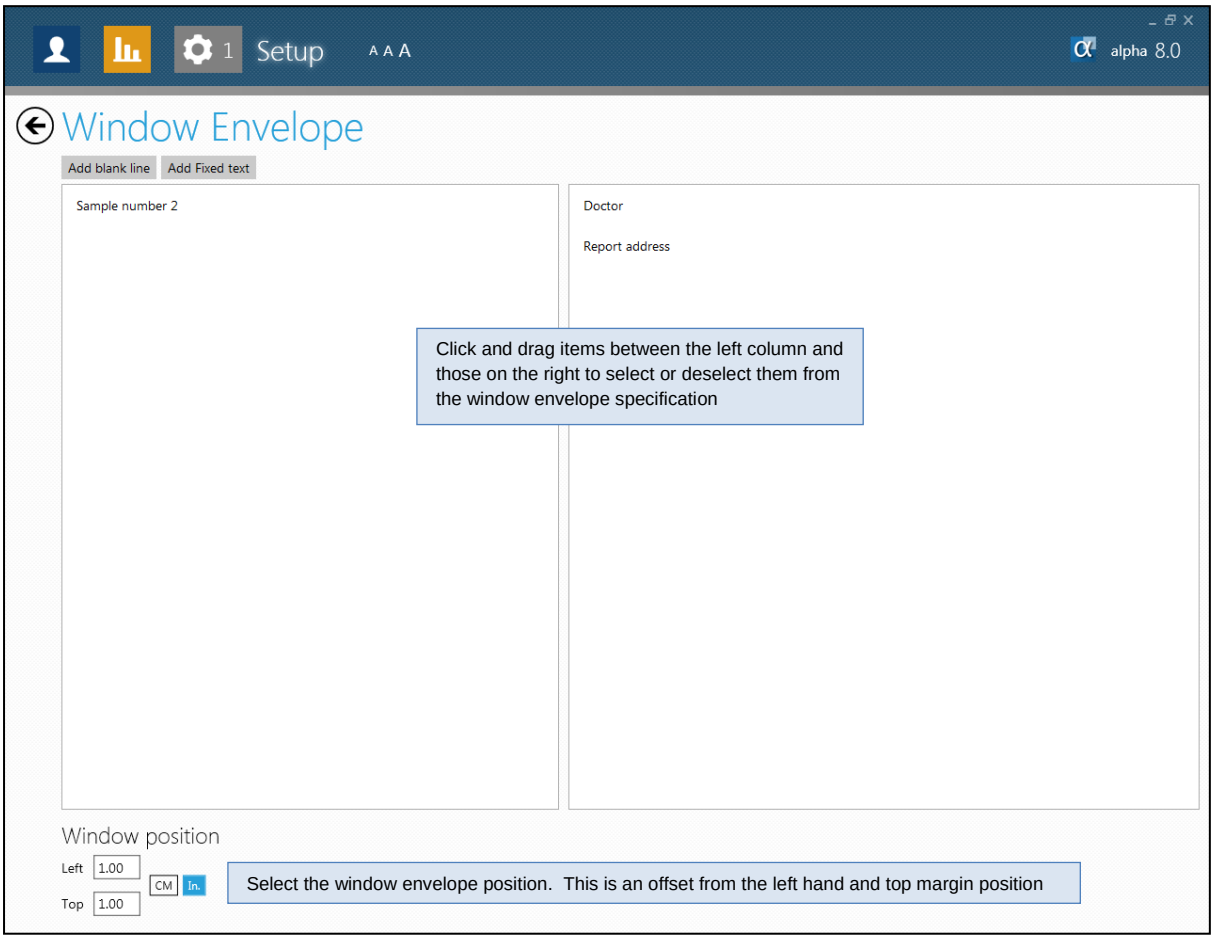


Figure 52: Window envelope setup

4 Patients screen

The **Patients** screen (Figure 53) shows a list of batch files together with a summary of the patient records contained in each batch. This screen provides facilities for adding patient records to batches, editing existing records, importing data into batches and printing information from batches.

The **Patients** screen also provides facilities for test and final reporting batches, searching for patient records in the **αlpha** database and if necessary correcting these records.

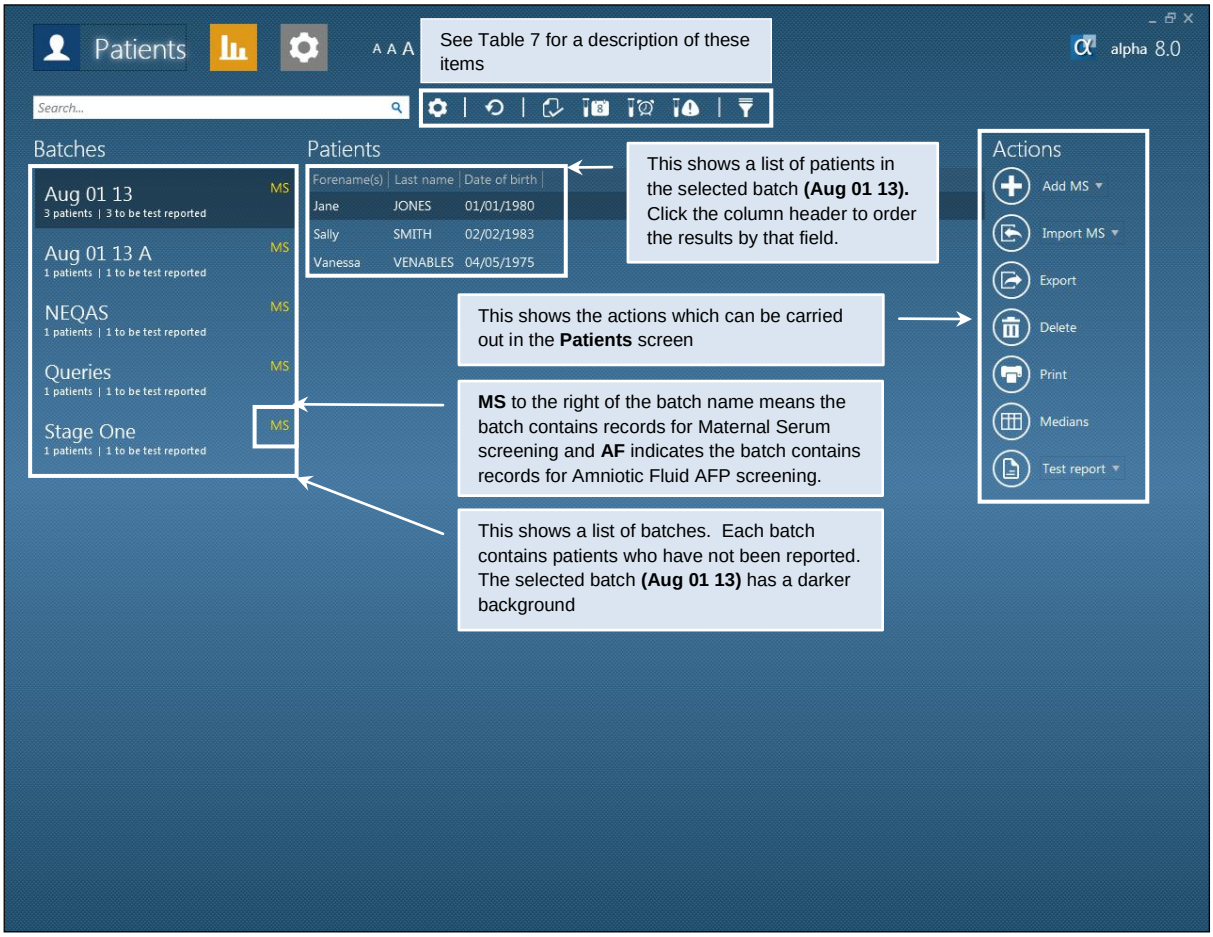


Figure 53: Patients screen

The purposes of the buttons next to the search box are given in Table 7

Table 7: Purpose of the buttons in the Patients screen

Button	Purpose
	Show the advanced search screen (Section 4.3)
	Refresh the list of patients.
	Show a list of patients having the integrated test which are ready to report (Section 3.11)
	Show a list of patients having the integrated test (who are not yet ready to report) with their ideal second sample date (Section 3.11)

Button	Purpose
	Show a list of patients having the integrated test whose second sample is now due (Section 3.11)
	Show a list of patients having the integrated test whose second sample is now overdue (Section 3.11)
	Group the patients according to the date when they were entered or the doctor or the address code. This grouping will also be used when a batch listing is made (See section 4.8)

Unreported patients can be moved to an existing batch, a new batch or deleted from the **Patients screen.** To do this, select the record by clicking on it and then dragging and dropping it on to the batch name, the  button or the  button respectively.

A consecutive group of patients can be selected by clicking on the first record, holding the shift key down on the keyboard, clicking on the last record and then dragging them to the desired location without releasing the shift key.

A non-consecutive group of patients can be selected by clicking on the first record, holding the ctrl key down on the keyboard, clicking on the other desired records and then dragging them to the desired location without releasing the ctrl key.

The columns shown on the Patient screen can be selected by right clicking on the title row and selecting the desired columns. A different set of columns can be chosen for the Integrated test list (Section 3.11) by pressing one of the Integrated test list buttons to shown an Integrated test list, right clicking on the title row and selecting the desired columns.

4.1 Data entry

You use **data entry** to manually enter information from new screening requisition forms and to edit records in an existing batch which has not been fully reported. When entering new screening requisition form information you can either enter them into a new batch or add them to an existing batch.

To start data entry in a new batch file press  . If **αlpha** has been configured for both MS-AFP and AF-AFP screening you will need to select **"Add MS"** from the drop down for MS data entry or **"Add AF"** for AF data entry.

To start data entry in an existing file, either double click the name of the batch or the name of the patient you want to edit.

αlpha displays the data entry screen showing the first record in the batch file (or the record you specified). If you are working with a new file, a blank record is displayed. An example of a data entry screen is shown in Figure 54. The appearance of your data entry screen depends on the prompts and screen layout you have selected (see Section 3.17). Table 8 shows the meaning of the various items in the data entry screen.

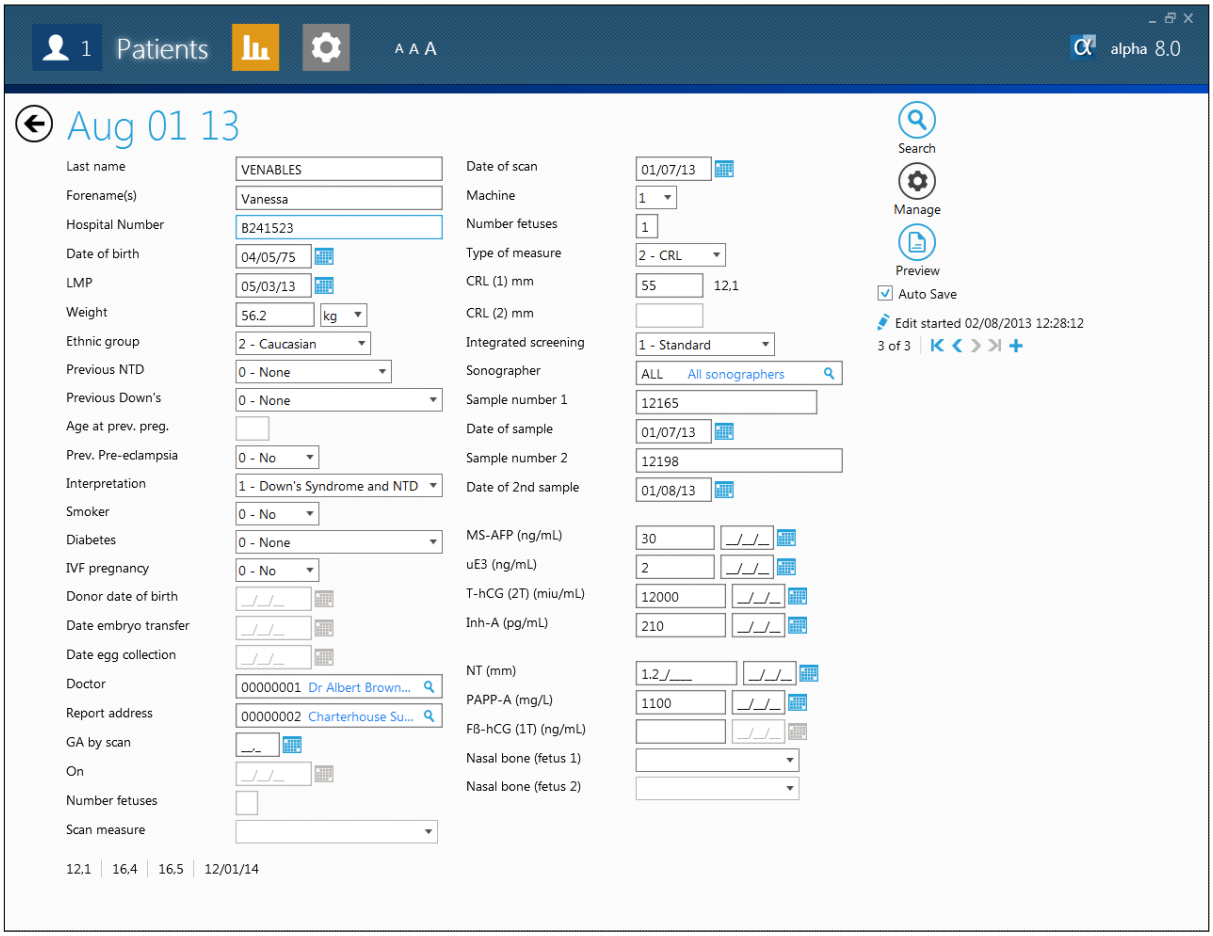
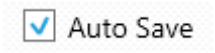
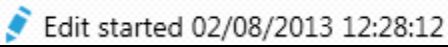


Figure 54: Data entry screen

Table 8: Meaning of items in the data entry screen

Item	Purpose
	This closes the batch. If you have not opened an existing batch file **αlpha** prompts you for a name for the new file. The default name is based on the current date (See section 2.7). Type a new name if you wish to change the name of the file.
	If the batch file contains more than one record, you can click **Search** to search through the file for the record you want. For example, to search for a record with surname SMITH, place the cursor on the *Surname* field, and then click **Search**. **αlpha** prompts you for the surname to search for. Click **Search** again to start the search and find the first record with surname SMITH. If the file contains more than one record with surname SMITH, you can find the next one by clicking **Search** again. You can use the same method to search on any field. **αlpha** uses a 'circular' search; when it reaches the end of the file, it resumes searching from the beginning of the file.
	This takes you to a screen where you can move or delete the current record in the batch or all records in the batch.
	This shows an interpreted report for the current record in the data entry screen. The preview report allows you to check the interpretation and helps to detect data entry

Item	Purpose
	errors. If a required item (such as the sample date) is missing, or if the record contains invalid data (for example, the sample date is after the current date), **αlpha** prompts you to correct the error.
	This setting controls how patient data is saved when moving between patients in the data entry screen. When **AutoSave** is not selected **αlpha** will prompt the user to confirm that the data should be saved. Otherwise, **αlpha** will automatically save the data By default, this is set to the same value selected in **"Save patient data in data entry"** in **User Options** (See section 3.20.1). This setting can be changed temporarily here to prevent an unwanted change from being automatically saved.
	This shows when editing started.
	The record navigator shows the record number and the total number of records in the batch. It also provides buttons to allow navigation backwards, ‹ forwards › and to the beginning ⏮ and end ⏭ of the batch. Press the + to add a new record to the batch.
	The meaning of each of these fields can be ascertained by hovering over them. In this case the first field (12,1) is the gestational age at the date of the first sample, the second field (16,4) is the gestational age at the date of the second sample, the third field (16,5) the gestational age today and the fourth field the expected date of delivery. The gestational age at the sample dates are shown in red if the sample has been drawn too early or too late. In non-integrated tests only one sample gestation is shown

When entering data:

- Surnames are always displayed in upper case. First names are displayed with the first letter of each name capitalised.
- For fields with coded values such as **IVF pregnancy** or **Previous NTD** you can either enter the required code directly or select the code from a drop down list.
- A date field appears to the right of each serum marker field. This field may be used to record the date of assay. This can be helpful in situations where the medians or weight correction equations may have been updated between the date of assay and the date of the report (for example, in centres that provide the integrated test). If the assay date is specified, **αlpha** bases the MoM value on the equations in effect on the date of assay. If the assay date is left blank, the current equations are used
- If the screen includes nuchal translucency (NT), a date field appears to the right of the NT field. This field may be used to record the date of NT measurement, if this is not the same as the date of crown-rump length (CRL) measurement. If CRL was not measured, the date of NT must be specified. If CRL was measured, and the date of NT is left blank, it is assumed to be the same as the date of CRL measurement

- A lookup button appears next to the Doctor, Report Address and Sonographer fields. Click the lookup button to access the list of doctors, addresses, or sonographers. *See Sections 3.3, 3.6 and 3.18* for more information on working with the doctor, address and sonographer lists.

4.2 Reporting

The production of reports in **αlpha** is a two step process.

Firstly, you create test reports. When you create test reports, **αlpha** checks each record for invalid data, and ensures that each record contains sufficient data to create a report. **αlpha** also looks for previous reports that may relate to the same pregnancy, or an earlier pregnancy in the same woman, and gives you the option to match such records together. Test reports give you an opportunity to review the results, and to correct any data entry errors, or suspect data, before issuing the final report.

When you are satisfied with the test reports, you create the final reports, which can either be printed or exported. When you create the final reports, the batch of records is automatically merged into the database.

Once the final reports are created, any further changes to each report may only be made using the **Edit** (**Correct and update)** options (Section 4.4). You use **Edit** to change reports that have already been issued, and to add information which was not available at the time of the original report, for example, ultrasound details or maternal weight. A message is added to the corrected or updated report, indicating that it is a revised version of a previously issued report.

The **Search and print** option (Section 4.3) provides additional copies of reports which can be printed, viewed on screen or exported.

4.2.1 Test reports

In order to start a Test Report, select the batch file you want to work with and click , if necessary selecting **"Test report"** from the dropdown. **αlpha** verifies the data in each record, and checks for potential matches with existing records in the database, and with unreported results.
The verification step checks that each item of data is valid and that sufficient information is available for each record to create a report. The matching process checks each record in the batch against records in the database to identify earlier reports that may relate to the same pregnancy, or to a previous pregnancy in the same woman (See section 4.2.2). Matching also checks each record against other unreported records to identify records that may have been entered twice in error.
If an error is found during the verification stage, **αlpha** indicates the type of error and offers you the choice of either editing the batch so that you can correct the error, or abandoning the test reports

If you choose to edit the batch, **αlpha** opens the data entry screen and displays the record containing the error. You can then edit the record in the usual way. When you close the data entry screen, **αlpha** continues with the test reports

Having verified the data and checked for potential matches, **αlpha** displays a preview of the report as shown in Figure 55. See Section 2.6.3 for further information about using the preview screen.

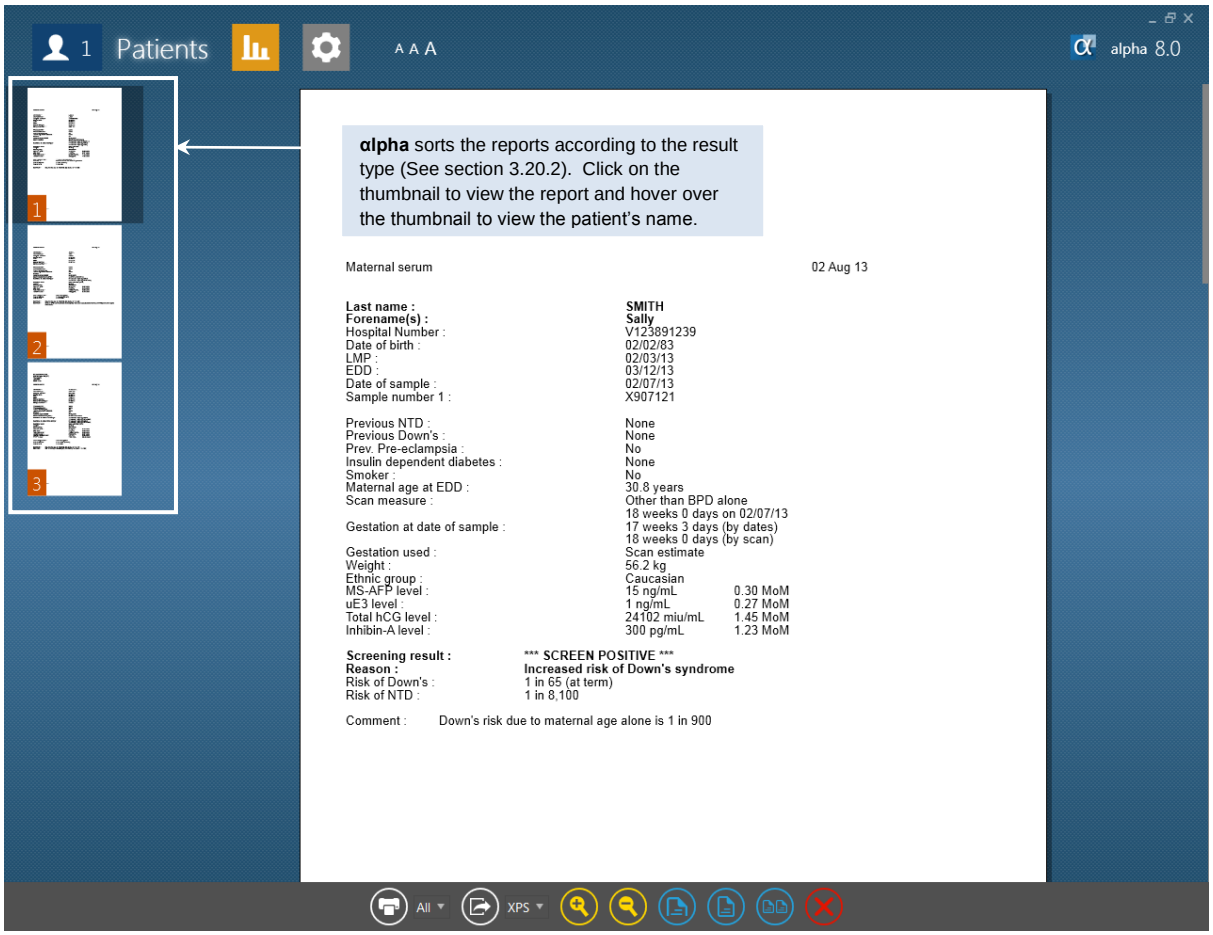


Figure 55: Test Report

If, after creating and checking the test reports for a batch file, you change one or more records in the file or add records to the file, you must create and check test reports again before you can create the final reports. When this happens, **αlpha** will ask whether you want to create test reports for all the records in the file, or just the records that were changed or added.

4.2.2 Checking for matches

αlpha will check for matches with reports for the same patient in the current pregnancy and previous pregnancies and also with unreported patients in all batches.

4.2.2.1 Current pregnancy (Repeat tests)

The check for matches is made on the basis of the woman's surname, ID code and date of birth. Any previously reported records with matching information in two or more of these fields will be considered to be potential matches if reported in the previous 13 weeks. When potential matches are found, **αlpha** displays the **Matches** window (See Figure 56), showing the record in the batch file being reported, and all potential matches found.

It is important to match records that relate to repeat samples, because estimating the risk correctly in a repeat sample requires that the marker levels in the previous sample be taken into account[17, 44]. If you do not match the samples, the repeat test is interpreted as if it were a first test and the risk estimate will be less accurate.

Current pregnancy and previous pregnancy matches (Section 4.2.2.2) are shown on the same **Matching** screen.

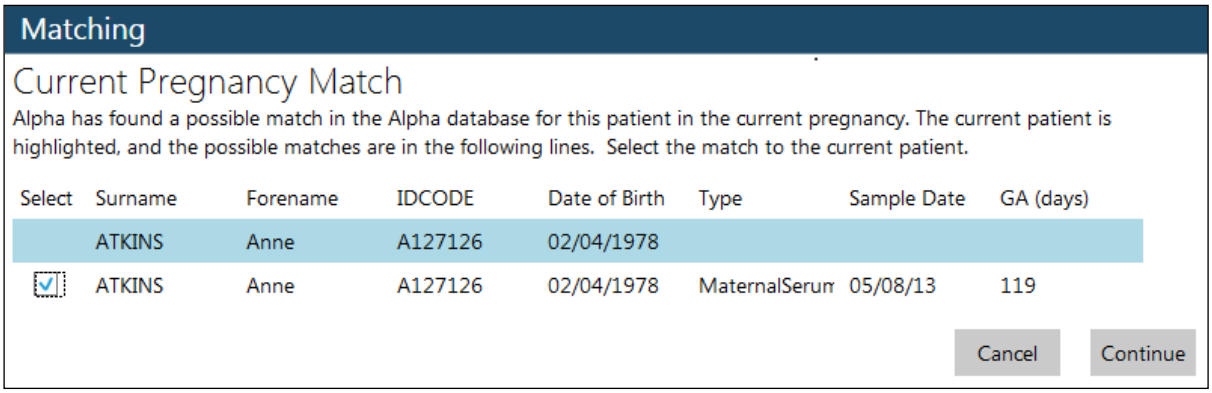


Figure 56: Repeat test

4.2.2.2 Previous pregnancy (Recurrent false positives)

Depending on the policy selected under section 3.1.11, **αlpha** may also check for previous reports that may relate to an earlier pregnancy in the same woman.

Women who have had a false-positive screening result in one pregnancy are much more likely to have a one in a subsequent pregnancy than women in general[50,59] **αlpha** can help to avoid this by adjusting serum marker levels in women who have been screened in a previous pregnancy and who have not had a previous pregnancy with Down's syndrome. If you use this facility, **αlpha** attempts to match each record in the file you are currently reporting with records in the database that may relate to the same woman, provided a previous pregnancy with Down's syndrome is not recorded. If potential matches are found, **αlpha** displays them (See Figure 57). If there is more than one matching pregnancy the most recent is shown as the default match. Earlier matching pregnancies are also shown in case the most recent match is a false match because of inaccurate recording.

Further information describing the method used to select patients for matching is given in section 3.1.11.

Current pregnancy (Section 4.2.2.1) and previous pregnancy matches are shown on the same **Matching** screen.

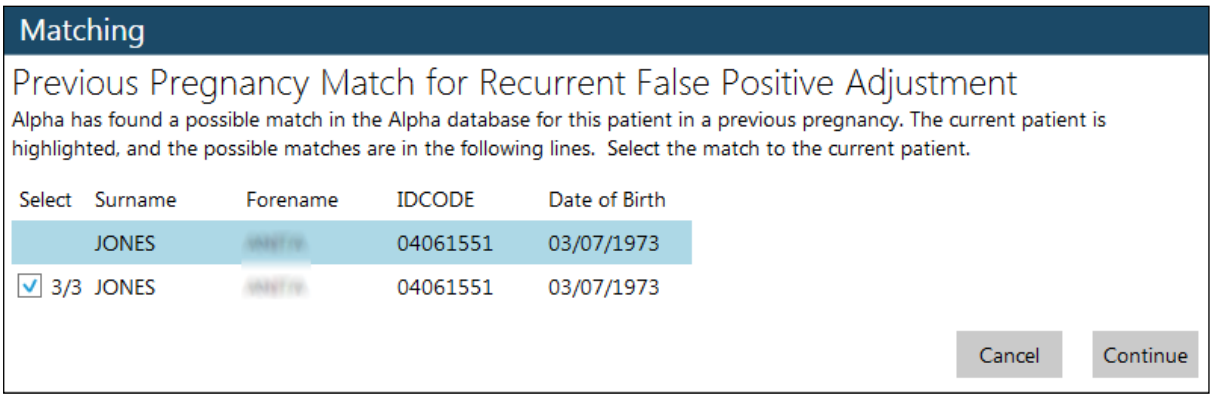


Figure 57: Recurrent false positive matching

4.2.2.3 Unreported records

As well as checking for matches with previously reported tests, **αlpha** checks for matches with records in the same batch file and in other batches which have not yet been reported. This feature is helpful for identifying patients who have been entered twice in error. If this occurs you should abandon the test report and delete one of the duplicate records before proceeding with test reports. Alternatively if the duplicate record genuinely relates to a repeat sample, the earlier sample should be processed before the later one. Repeat samples cannot be processed in the same batch file. The record for the initial sample must be moved to another file and reported, before processing the repeat sample.

4.2.2.4 Breaking and making matches after creating test reports

When you create a test report, and potential matches are identified between one or more records in the batch file and previously reported results, **αlpha** prompts you to select whether or not to accept of each potential match. **αlpha** remembers your selections, and does not prompt again if you create the test report again (for example, if you later identify and correct data entry errors in the batch file). This avoids having to repeatedly accept or reject matches when test reports are created more than once.

If you subsequently need to change one of your selections (for example, because you accepted the match in error) you can force **αlpha** to prompt you again by editing the corresponding record. To do this, open the batch file and locate the record for which you want to break or make a match. Change the contents of any field (for example, the woman's name), highlight any other field, then move back to the field you changed and change it back to its correct value. Then close the batch and create the test report again. **αlpha** will prompt you to accept or reject the match for the record you edited.

4.2.3 Final reports

When you are satisfied with the test reports, you create final reports which can be printed or written to an XPS or **αlpha** export file. You can only create final reports if test reports have been created for records in the batch file. Once this has been done, you will be able to select **"Final report"** from the dropdown next to the  button. **αlpha** then displays a preview of the final reports (See Figure 58).

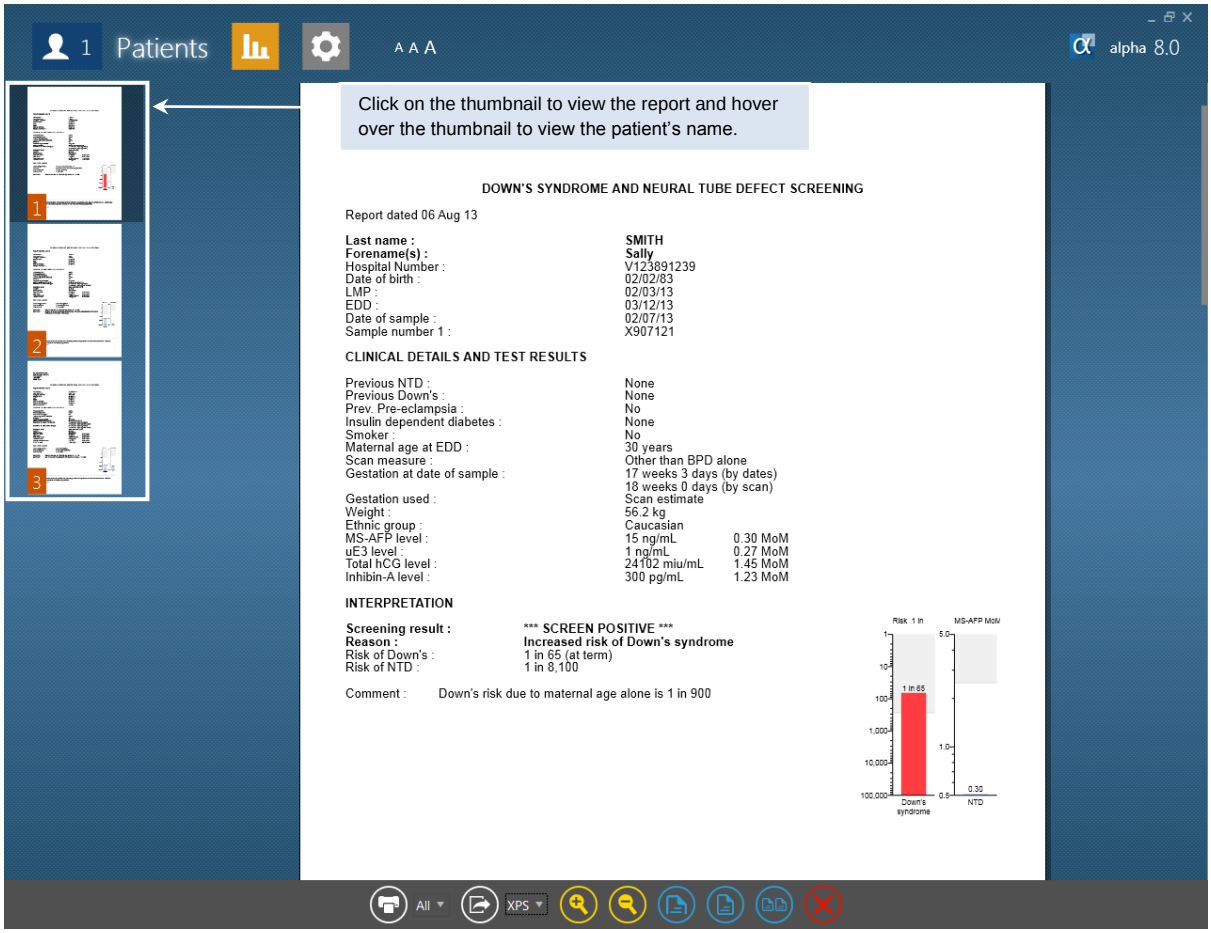


Figure 58: Final report

The print and export buttons include the special functions shown in Table 9 when used for final reporting.

Table 9: Print and export options available in final reporting

Button	Drop down item	Purpose
	All	Print all reports
	Positive only	Print only positive reports
	XPS	Write reports to one XPS file containing all the reports.
	Individual XPS	Write each report to an individual XPS file (See section 3.20.5)
	Standard	Write reports to a standard export file (See Section 4.2.6.1). Only shown if Standard export report is selected in Report Export Format Selection (Section 3.20.3).
	Packet	Write reports to a packet export file (See Section 4.2.6.2). Only shown if Packet export report is selected in Report Export Format Selection (Section 3.20.3).

When the final reports have been printed or written to file using the options in Table 9, **αlpha** returns to the final report preview screen. You can make further selections at this point to create extra copies of the reports, (for example, if you require both printed and exported reports).

Once you close the final report preview screen:

- The reports are merged into the **αlpha** database.
- The results, if requested, are written to the export text file (Section 3.9).
- The batch file is deleted.

If the final reports are not printed or written to file, or only positive reports are printed, these operations are not carried out and the reports remain in the batch file.

Once the reports have been merged into the database you can obtain additional copies of the reports (either printed or in export file format) using the **Search** option (See section 4.3).

4.2.4 MoM values printed on reports

Maternal serum MoM values appearing on **αlpha** reports include adjustment for weight, in cases where the woman's weight is recorded. **αlpha** may make certain other adjustments to the MoM values, for example, in twin pregnancies, diabetic women, women who conceive by IVF, women who smoke, and women screened in a previous pregnancy. (See Appendix P *Factors used for adjusting MoM values)* While these adjusted MoM values are used in estimating the risk of having an affected pregnancy, and in classifying the result as screen positive or screen negative, the reported MoM values do not include these other adjustments unless the parameter **Print Adjusted MoMs** is set. If **Print Adjusted MoMs** is set to **Adjust** the MoM values on the report will be adjusted in twin pregnancies, IVF pregnancies, for women who smoke and for diabetic women.

4.2.5 Sequential testing

αlpha can be used to interpret sequential testing which allows early completion of screening with very high risk pregnancies identified in the first trimester. A high risk cut-off is set for the first trimester test. (See section 3.1.6 for further information). Nearly all women proceed to the full Integrated test.

After a batch has been test reported and the close button on the preview screen selected, tests that were positive in the first trimester are automatically identified. These patients can be separated into another batch for final reporting (see section 4.2.3) as shown in Figure 59. Other patients continue to the full Integrated test and remain in the batch until the second trimester samples are available. The Integrated test options (see section 0) can be be used to set up reminder lists of patients whose second Integrated Test sample is overdue.

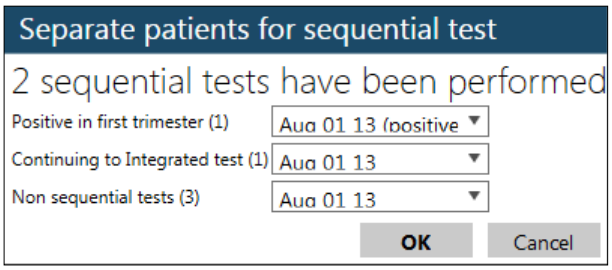


Figure 59: Separating sequential tests

If hCG is measured in both the first trimester and second trimester of sequential testing, the first trimester hCG measurement is not reused in the calculation of the Integrated test risk estimate.

The report summary (see Section 5.10) can be used to monitor the number of sequential tests that were completed at the first trimester, and how many proceeded to the full Integrated test.

4.2.6 Export Report Formats

In addition to exporting results to a text file when the final report is made (see Sections 3.9 and 4.2.3) **αlpha** can export the reports to a file in either **Standard** or **Packet** Export format. Reports can be exported in these formats when a final report is made (see Section 4.2.3 and Table 9) or after a search has retrieved the report from the **αlpha** database (see Section 4.3)

4.2.6.1 Standard Export

A report in the **Standard** format is a copy of the printed report written to a text file. Text formatting (such as boldening and underlines) and the riskometer are not included in this format. Figure 60 shows the report in Figure 2 exported in **Standard** format. This format may be useful when a laboratory information system needs to store the full text of the report.

```
Dr Albert Brown MD
The Surgery
24 Park Lane
LONDON
NE3 ZA9

DOWN'S SYNDROME, NEURAL TUBE DEFECT AND PRE-ECLAMPSIA SCREENING

Report dated 08 Jan 14

Last name :                         JONES
Forename(s) :                       Jenny
Hospital Number :                   1342ZYD
Date of birth :                     02/03/82
LMP :                               10/09/13
EDD :                               20/06/14
Date of sample :                    07/12/13
Date of 2nd sample :                07/01/14
Sample number 1 :                   52413
Sample number 2 :                   52601

CLINICAL DETAILS AND TEST RESULTS

Previous NTD :                      None
Previous Down's :                   None
Prev. Pre-eclampsia :               No
Insulin dependent diabetes :        None
Smoker :                            No
Maternal age at EDD :               32 years
Scan measurement (CRL) :            55.4 mm on 07/12/13
Gestation at date of 1st sample :   12 weeks 4 days (by dates)
                                    12 weeks 1 days (by CRL scan)
Gestation at date of 2nd sample :   17 weeks 0 days (by dates)
                                    16 weeks 4 days (by CRL scan)
Gestation used :                    Scan estimate (CRL)
Weight :                            65.2 kg
Ethnic group :                      Caucasian
MS-AFP level :                      30.1 ng/mL    0.77 MoM
uE3 level :                         2.1 ng/mL     0.75 MoM
Total hCG level :                   21000 miu/mL  1.27 MoM
Inhibin-A level :                   210.1 pg/mL   0.96 MoM
Nuchal measurement :                1.2 mm        0.96 MoM
PAPP-A level :                      12.11 mg/L    1.10 MoM

INTERPRETATION

Screening result :     Screen negative
Risk of Down's :       1 in 9,000 (at term)
Risk of NTD :          1 in 7,000
Risk of Pre-eclampsia :1 in 60

Comment :  Down's risk due to maternal age alone is 1 in 720
Comment :  Not in the high risk category for trisomy 18 (risk < 1 in 100)
Comment :  Not in the high risk category for trisomy 13 (risk < 1 in 100)


--------------------------------------------------------------------------------
A screen negative result does not exclude the possibility of Down's syndrome,
 a neural tube defect or pre-eclampsia, because screening does not detect all
 affected pregnancies
```

Figure 60: Report exported in standard format

4.2.6.2 Packet Export

In **Packet** format each element of the report is defined by a packet number and the fixed and variable parts of the text are presented in a specified format. Figure 61 shows part of the report in Figure 2 exported in **Packet** format. Full details of **Packet** format are given in *Appendix* I *Packet export report format.* This format may be useful when a laboratory information system prepares a screening report in a bespoke format using the messages and details provided in the **αlpha** screening report.

```
$090,00,01,01
/Dr Albert Brown MD/
$095,00,04,04
/The Surgery/
/24 Park Lane/
/LONDON/
/NE3 ZA9/
$005,01,01,02
?DOWN'S SYNDROME, NEURAL TUBE DEFECT AND PRE-ECLAMPSIA SCREENING?
/Report dated 08 Jan 14/
$030,01,01,02
?Last name?
/JONES/
$035,01,01,02
?Forename(s)?
/Jenny/
$050,01,01,02
?Hospital Number?
/1342ZYD/
$055,01,01,02
?Date of birth?
/02/03/82/
$060,01,01,02
?LMP?
/10/09/13/
$067,01,01,02
?EDD?
/20/06/14/
$070,01,01,02
?Date of sample?
/07/12/13/
$071,01,01,02
?Date of 2nd sample?
/07/01/14/
$085,01,01,02
?Sample number 1?
/52413/
$100,01,01,02
?Sample number 2?
/52601/
$120,01,01,02
?Previous NTD?
/None/
$125,01,01,02
?Previous Down's?
/None/
$127,01,01,02
?Prev. Pre-eclampsia?
/No/
$130,01,01,02
?Insulin dependent diabetes?
/None/
$131,01,01,02
?Smoker?
/No/
```

Figure 61: Part of report exported in packet format

4.3 Searching

You use the search option to reprint copies of reports from the database or to find patient records that have been entered but not yet reported.

4.3.1 Basic search

A simple search is performed by entering a search term in the text box in the patients screen (Figure 53). For example the search for “JONES” in Figure 62 finds one patient in a batch and one patient in the **αlpha** database with the last name “JONES”.

If text is entered as a search term **αlpha** will search all text fields for exact matching entries or for entries with begin with the search term. For example, the search term JEN would return matches for a record with first name JENNIFER and also a record with last name JENKINS.

If a date is entered as a search term **αlpha** will search all date fields for a matching date.

Records found in the **αlpha** database are shown under the **Search Results** heading **Reports** and records which have not yet been reported are shown under the heading **In Batches.**

Double clicking on the patient’s name will show the screening report (for a report in the **αlpha** database) or show the data entry screen (for unreported patients).

Press  to clear the search results.

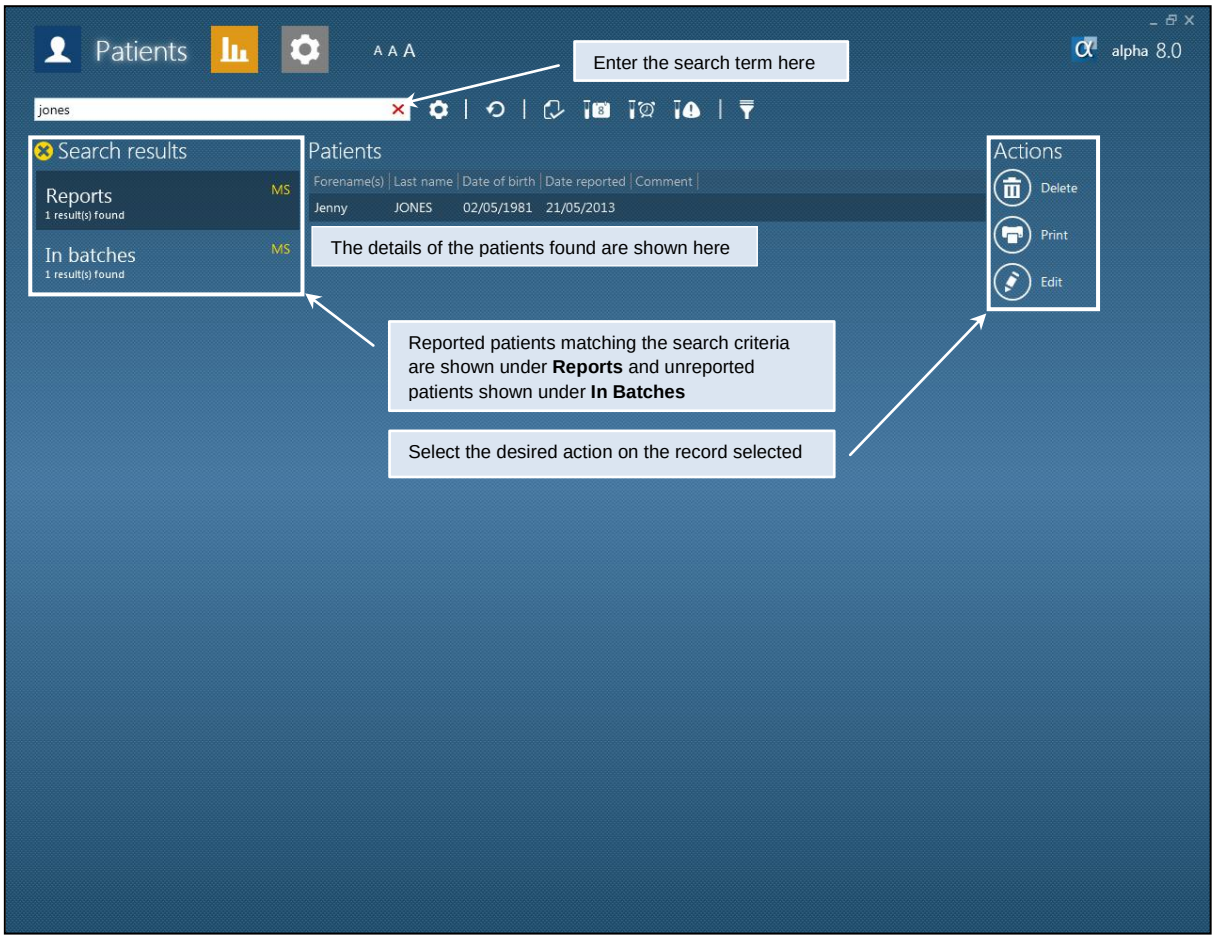


Figure 62: Search

4.3.2 Advanced search

Press  to show the advanced search screen (Figure 63). The advanced search screen allows you to specify search terms for any of the fields in the database.

You can use wildcards for any field allowing text entry. The wildcard "*" matches any number of characters including none. For example if you type "BROWN*" into the last name field, αlpha will find all records where the last name begins with "BROWN" (for example BROWN, BROWNING).

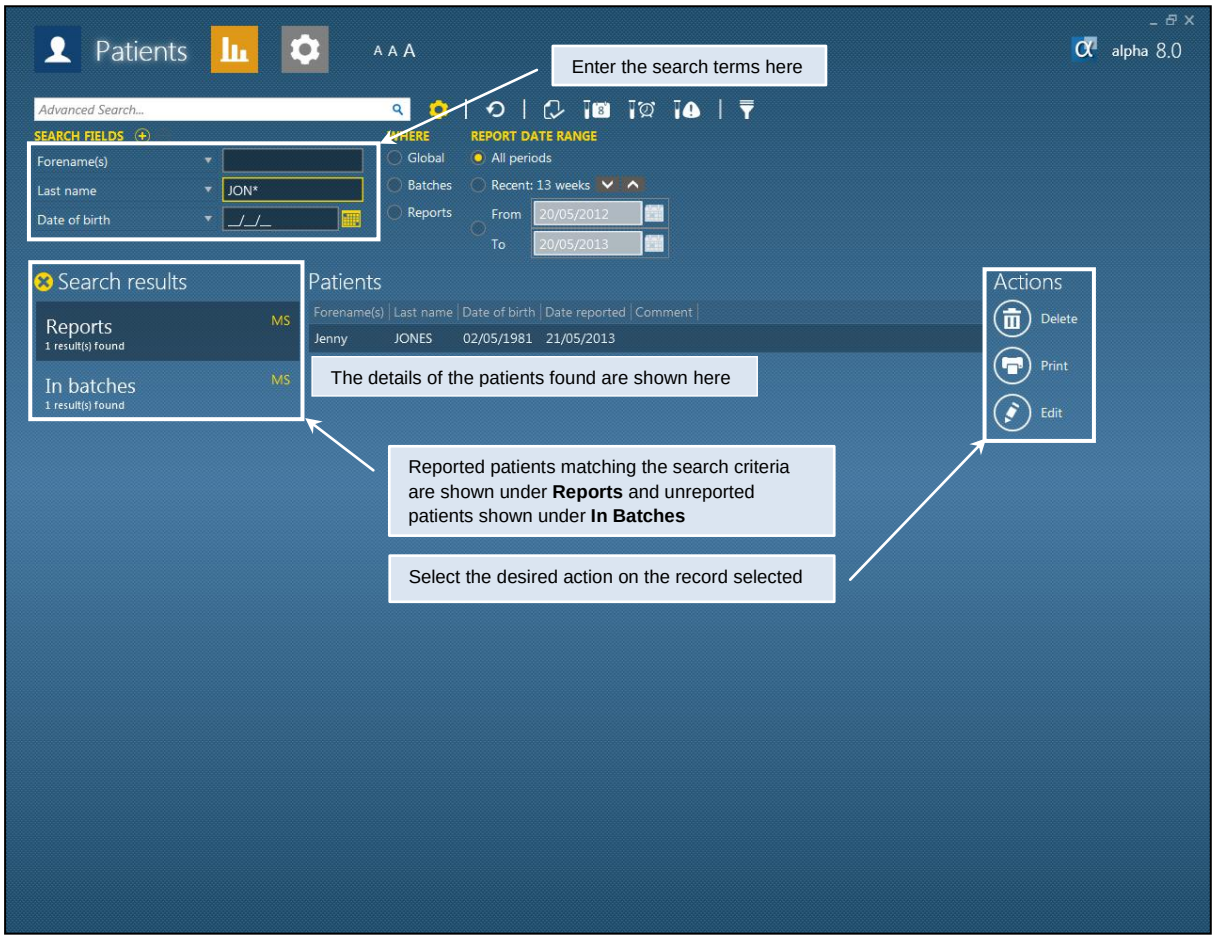


Figure 63: Advanced search

You can specify that records are searched for globally (in the **αlpha** database and in batches), in batches only or as reports (i.e. in the **αlpha** database). In addition, the report date range can be specified so that all periods (i.e. without restriction on date), recent reports (reports made within a specified number of weeks) or in a specified date range.

Any field in the **αlpha** data entry screen can be added as a search field. To do this, select the dropdown to the right of the search field and a list of the available search fields will be shown. If you wish to add further search fields press the  button. Fields can be deleted with the  button.

Records found in the **αlpha** database are shown under the **Search Results** heading **Reports** and records which have not yet been reported are shown under the heading **In Batches.**

Double clicking on the patient's name will show the screening report (for a report in the **αlpha** database) or show the data entry screen (for unreported patients).

Press  to clear the search results.

4.4 Edit reports (Correct and update)

You use **Edit reports** (**Correct and update)** to create MS or AF reports that are either corrections or reinterpretations (updates) of existing reports. **αlpha** classifies each report generated with this option as either a correction or an update. The new report carries a heading indicating that it is a correction or an update of a previous report. MS reports are classified as updated reports after the addition of ultrasound scan. AF reports are classified as updated after the addition of ultrasound scan, AchE or PchE results. Any other change is classified as a correction. A report cannot be corrected and updated at the same time. **αlpha** will use the settings of the coefficients and parameters on the date of the original report for the corrected or updated report.

To edit a report, you first search the database for the original report as described in section 4.3 and then select  . The data entry screen for the original report is now shown and can be modified as required (Figure 64).

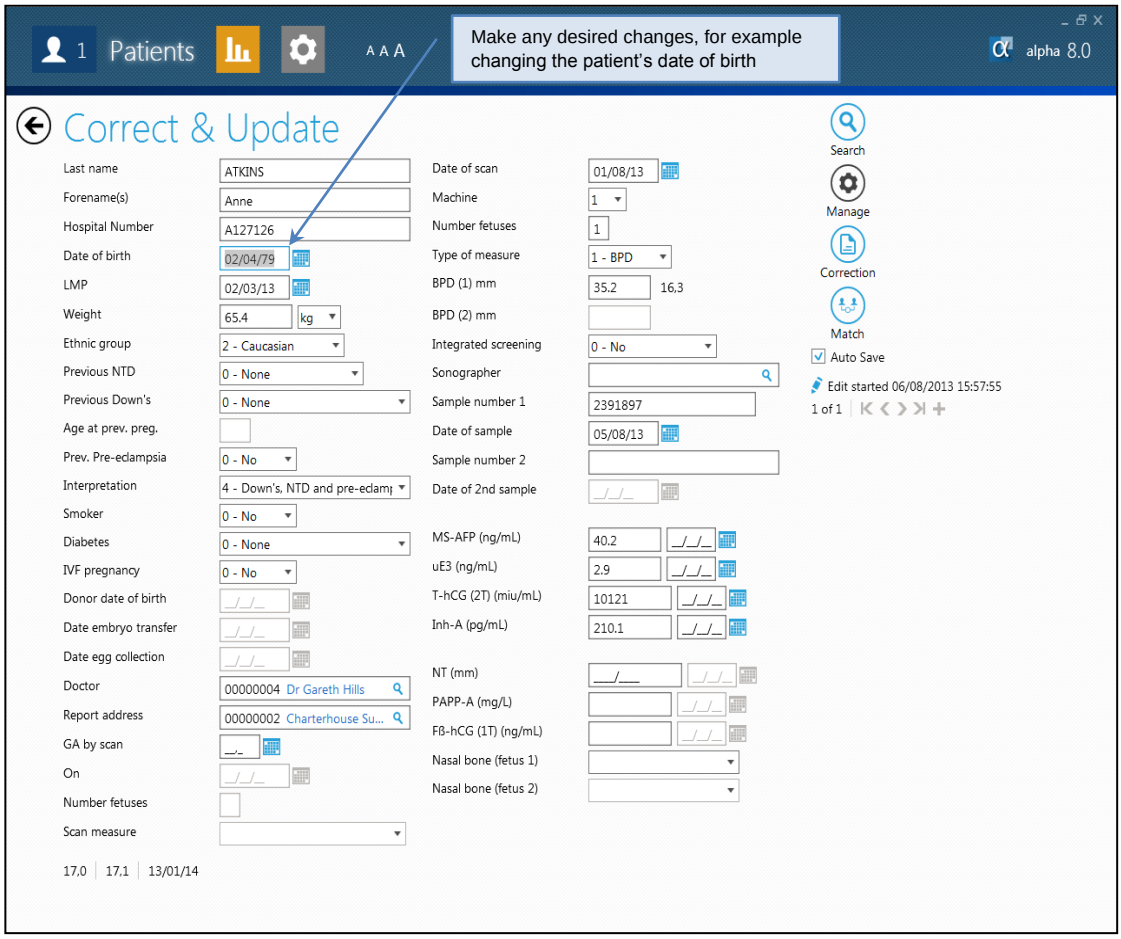


Figure 64: Edit report

When you have made the required changes, press **Correction** to preview the revised report and to print and edit it (See Figure 65).

NOTE: The revised report is only saved in the αlpha database if it is printed or exported. It is not sufficient to simply to view the report.

Before you review the revised report, you can create a new match by pressing **Match** . If the report was already matched, you can break the match by pressing **Break Match.**

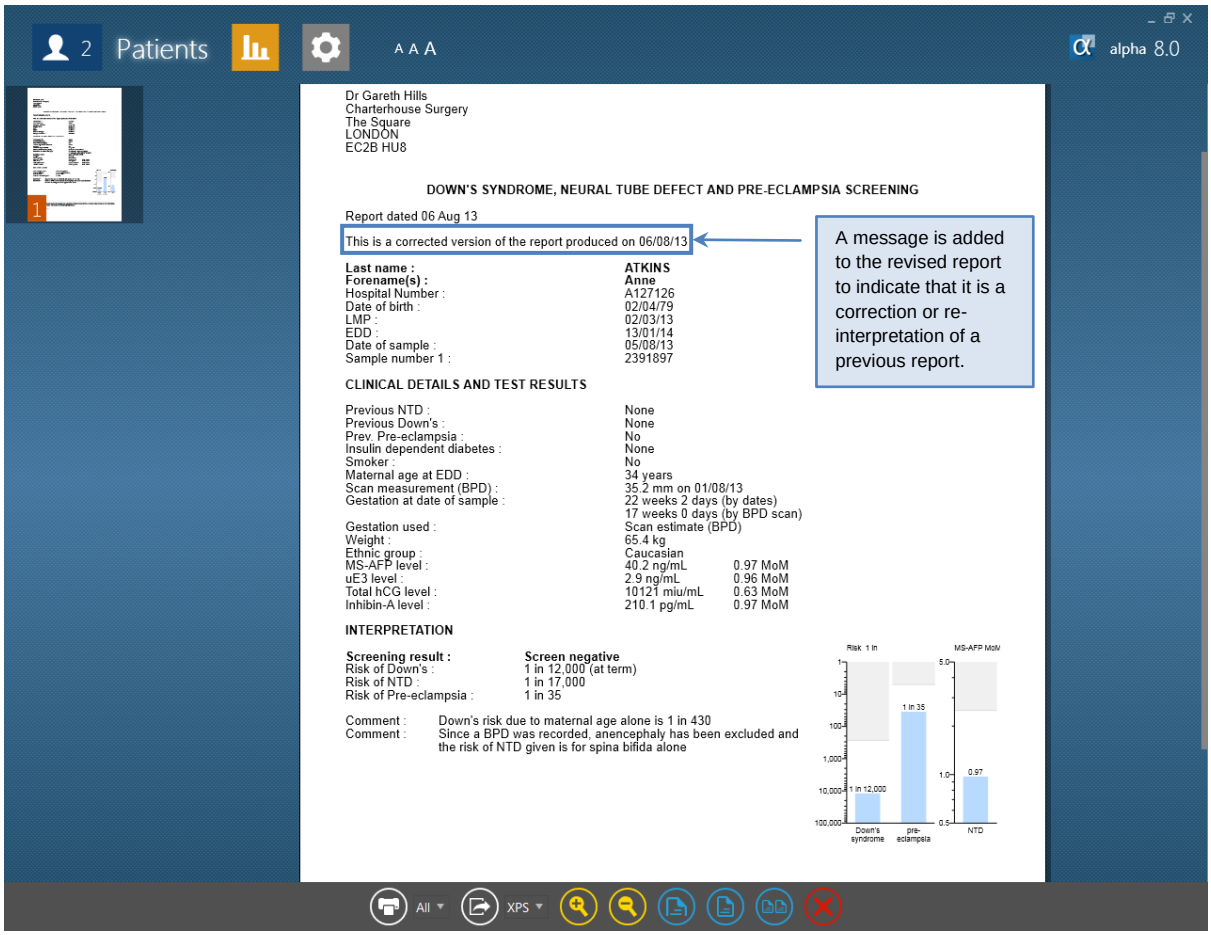


Figure 65: Report correction

When you create a corrected or updated report, **αlpha** prompts you to enter a comment. You might choose to use this feature to record further details of the correction or update, such as what prompted it. The comment is optional, however if you enter a comment, it is stored in the **αlpha** database. The name of the user who made the change is also recorded in the database.

These comments can be reviewed in the list of patients in the **Patients** Screen. You can also access them by exporting the **Comment** field with Analyze-It (Section 5.2).

αlpha treats reports for each pregnancy as a series. Most report series consist of a single report. However, where repeat tests are matched to previous tests, or a corrected or updated report is issued, the report series consists of two tests. Further repeat tests, corrections, or updated reports can increase the number of reports in a series. **αlpha** only allows you to work with the latest report in a series, so any corrections or updates are made to the last report in a report series.

4.5 Import

4.5.1 Import from text file

You can use **Import** to create a batch file, or add records to an existing batch file, from an external text data file, without having to enter the data manually with **Data entry**. You can import all or part of the information for each record. The information you import is defined using the **Import settings** option (Section 3.10).

To import data press the **Import** on the Patients screen, if necessary selecting **MS Import** or **AF Import** from the drop down. In the import screen, select the file to import and press the **Next** button. A screen similar to that shown in Figure 66 will be shown.

When **αlpha** imports data, it checks each item of data for errors. Errors are classified either as severe errors or warnings, and **αlpha** will display the number of each type of error found. For example, a sample date in the future, or an invalid date such as 31 September, would be classified as a severe error. An implausible entry, such as a weight of 220 kg, or an LMP date less than 8 weeks in the past, would be classified as a warning. **αlpha** will also check if the imported data matches any records which have not yet been reported. This prevents any records being unnecessarily reported more than once.

αlpha shows the number of records which have been read in the import file and indicates the number of warnings, errors and matches. Details of the warnings and errors can be found by double clicking on the record. The details of any match found are shown with the record. A check box is used to indicate if the record is to be stored in the batch. By default, all records except those with errors and matches are set to be imported. Press the **Import** button to save the data in a batch.

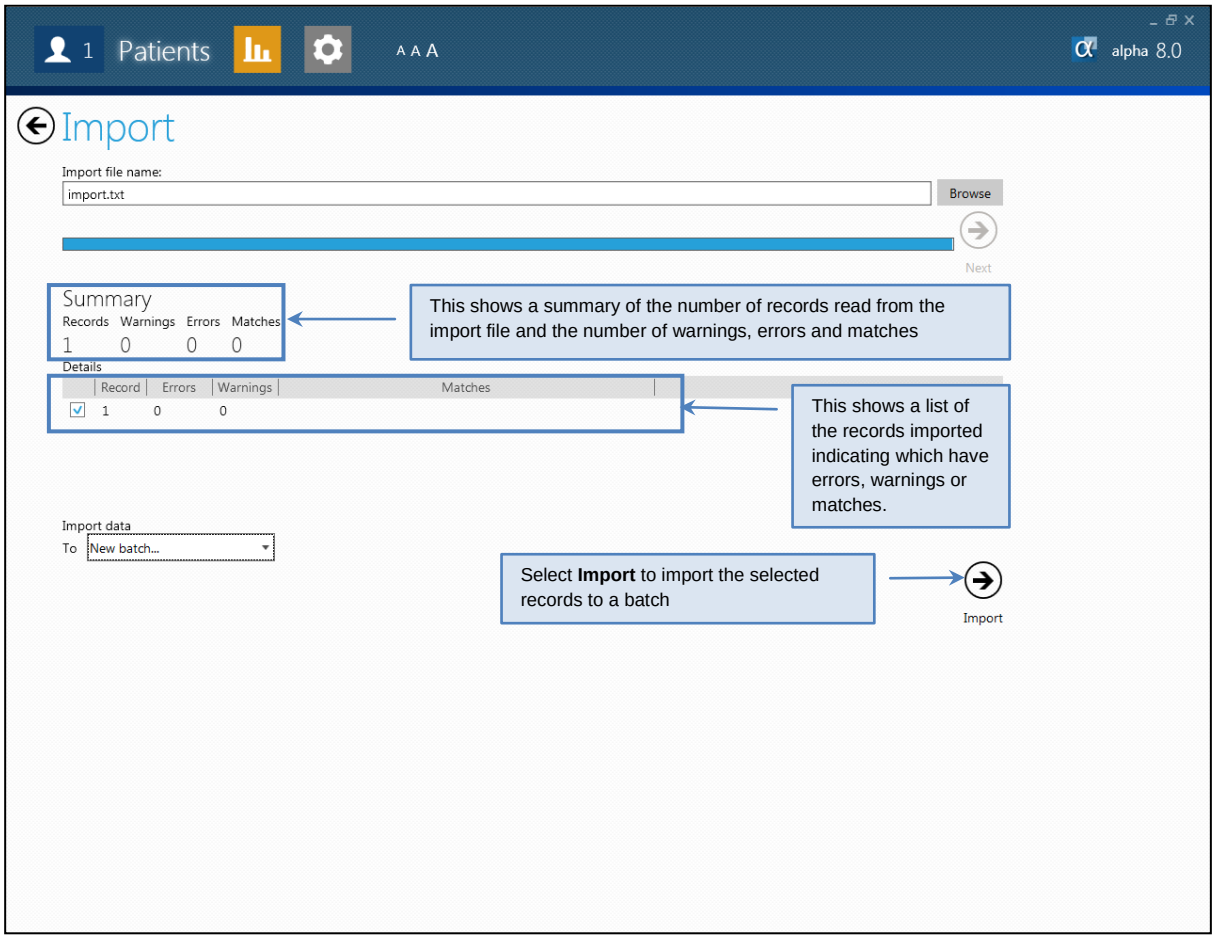


Figure 66: Import data

4.5.2 Analyser import

If **Analyser Import** has been configured (See *section* 3.4 *Analyser import*) this option will be shown in the dropdown list for the **Import** button**.** When this option is selected the screen shown in Figure 67 is shown. This allows you to select the filenames containing the marker measurements you wish to import. Press Next to import the measurements and to show the Data Screen (Figure 68). This shows the field used for matching (Sample Number in this example), the marker measurements read from the import file and the matching patient's name and ID Code (PatientID in this example) in the **αlpha** batch files together with the current marker measurements stored in the batch file (if any). The screen also shows any errors found when reading the import files and any lines in the import file for which matching record in the **αlpha** batch files were not found. Press Transfer to transfer these values to the batch file.

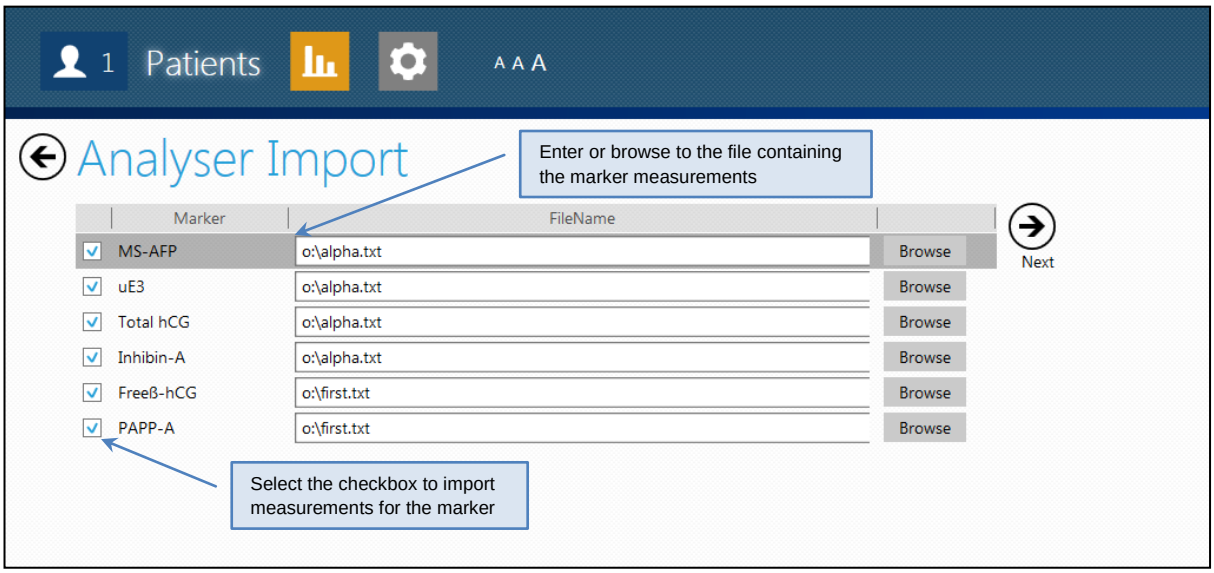


Figure 67: Analyser Import File Selection

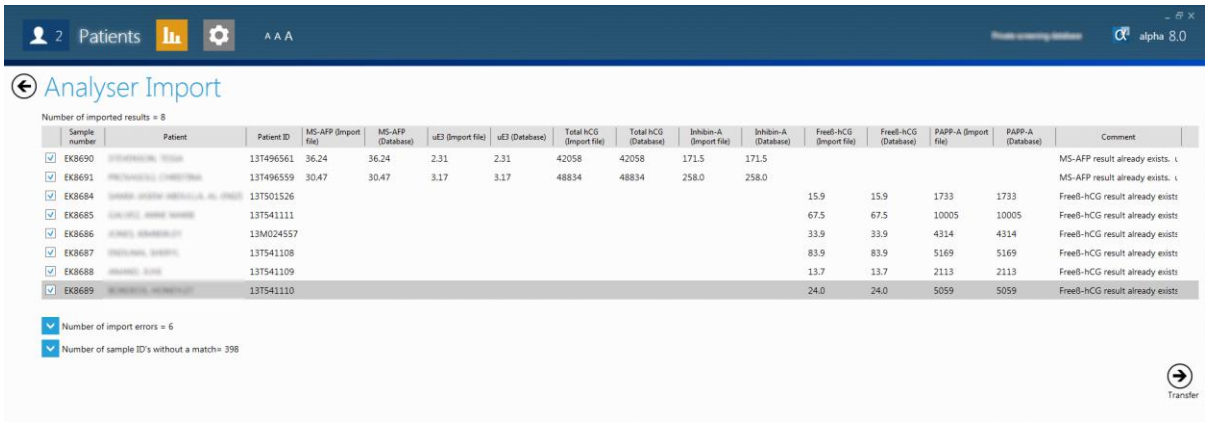


Figure 68: Analyser Import Data Screen

4.6 Export

The data stored in the records in a batch file can be exported to a text file. This can be useful if the data entered into **αlpha** needs to be reviewed elsewhere, for example for quality control. The **export** button will only be present if a file ExportFieldsMS.txt (for MS batches) or ExportFieldsAF.txt (for AF batches) is present in the folder containing the **αlpha** software. This file contains a list of the database table column names which are to be exported. When this button is pressed, you will be prompted for a filename and the specified data for the currently selected batch will be exported.

4.7 Delete

Unreported and reported records can be deleted from the Patients screen.

4.7.1 Unreported records

An unreported record can be deleted by selecting it on the Patients screen and dragging it to the **Delete**  button. Unreported records can also be deleted in the data entry screen (See Table 8)

4.7.2 Reported records

To delete a record, first find it using the search features (See Section 4.3) and then press the **Delete**  button. All records in a report series related to the selected record will be deleted (See Section 4.4). Deleted records remain in the database but are no longer available for search, correct and update, and they are also excluded from all tabulations and summaries

4.8 Print

The **Print**  button changes its behaviour depending on the context in which it is selected.

Following a search (Section 4.3) a report stored in the **αlpha** database can be retrieved and shown in the preview screen by pressing the print button. If you select more than one report from the search, all the reports selected will be shown in the preview screen when the print button is pressed.

If a batch is selected and the print button pressed a summary of the data in the batch is shown in the preview screen. Also, following a search (Section 4.3) a summary of the records found in batches can be shown in the preview screen by pressing the print button.

The records identified using the Integrated test options (Section 3.11) can also shown in the preview screen by pressing the print button.

For the summary of data in the batch and the Integrated test list the columns shown, the column used for sorting and the column used for grouping records can be selected (See Section 3.20.6).

4.9 Medians

As well as tabulating median values for reported results *(See Section 5.2)* you can also examine tabulations of the medians in a batch of unreported results, using the **Medians**  option in the **Patients** screen. In large screening programmes, with sufficiently large batch sizes, this can be helpful in identifying assay problems, and in correcting any problems identified, before a batch of screening results is reported. If the overall median MoM for a batch of results is significantly high or low (outside the 95% confidence interval around 1.0 MoM) this may indicate an assay error. The appropriate corrective action, in such cases, might be to identify the cause of the error, and having corrected it, re-assay the batch of samples before reporting the results. Alternatively, it may have arisen because of a change in the assay (for example, a new assay lot number, or a change in laboratory conditions). In such cases, you could perform a regression of the tabulated data from the batch file, and update the coefficients of the median equation to allow for the change in the assay (provided, of course, that the regression is based on a sufficiently large number of samples, and is judged to be satisfactory).

5 Statistics screen

The **statistics** screen provides facilities with which you can:

- Generate a wide range of tabulations, graphs and summaries to help in monitoring the performance of your screening programme.
- Perform regressions to obtain coefficients for equations used in estimating the median marker level for a given gestational age, and in correcting serum marker levels for maternal weight
- Extract records from the database for analysis by another software package.

The options available are:

Analyse-it (Section 5.2) provides a powerful facility for users to analyse data collected by **αlpha**.

Data transfer (Section 5.3) exports data collected by αlpha to a text file.

Median Analysis (Section 5.4) provides facilities for producing graphs of median MoMs with time
Missing information (Section 5.5) provides a facility for creating tables of information which was missing from patient records

Nuchal Translucency monitor (Section 5.6) provides a facility for monitoring sonographer specific nuchal translucency medians.

Outcome (Section 5.7) provides a facility for entering pregnancy outcomes and for the complete validation of your screening programmes.

Population (Section 5.8) shows the maternal age distribution in your screened population.

Regressions (Section 5.9) provides facilities for deriving regression equations for the expected marker median levels.

Report summary (Section 5.10) provides a breakdown of reports according to the screening results

Risk analysis (Section 5.11) provides a facility for investigating the cut-off required for a given screen positive rate.

Screening performance (Section 5.12) provides facilities for calculating the expected screening performance for any screening test.

Tabulations (Section 5.13) provides facilities for monitoring the variation of marker levels with gestational age or CRL. Tabulated data can then be used in the regressions facility (Section 5.9) to calculate new values for the regression equation coefficients.

5.1 Automonitor

Automonitor provides an overview in a single screen of the performance of your screening programme when the **Statistics** screen is shown (Figure 69). It provides an immediate warning of any issues which may need further investigation and complements the other statistical and monitoring features provided by the **Statistics** options.

Automonitor automatically selects a date to start monitoring so that at least 250 reports are analysed from the selected date to today. It analyses the reports in this date range and presents the results in a number of sections on the **Automonitor** screen which are summarised below:

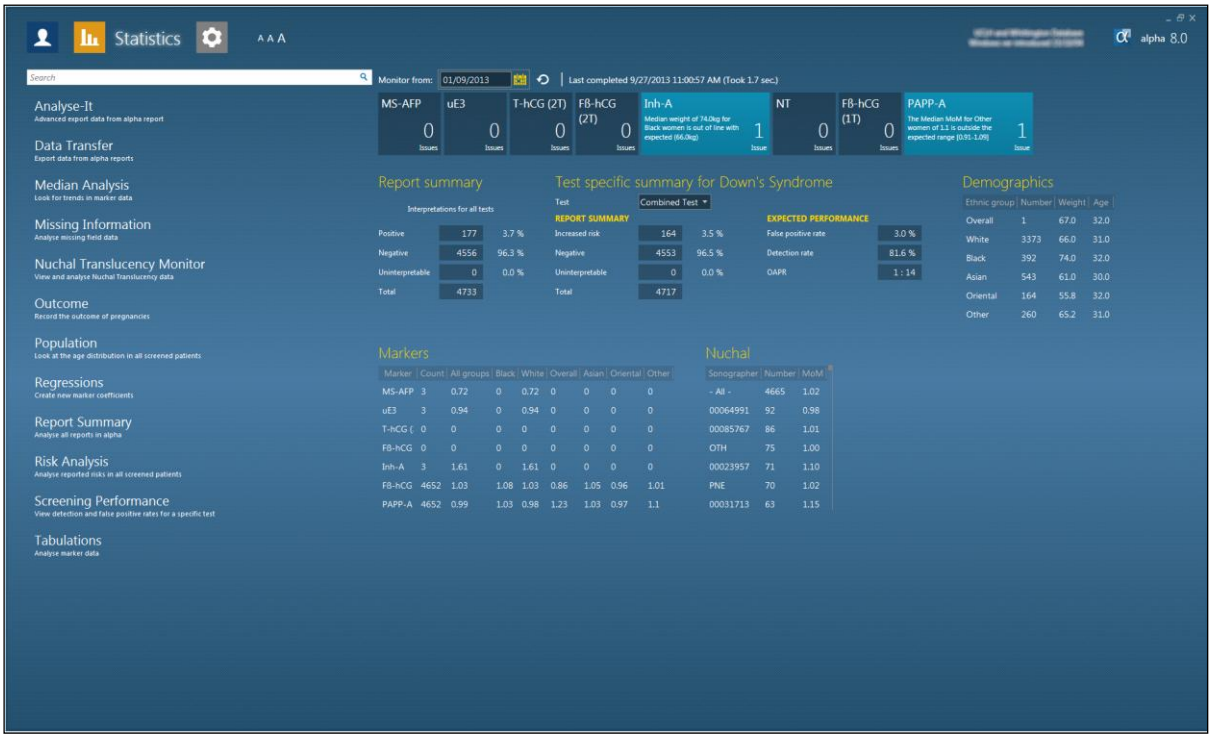


Figure 69: Statistics screen showing Automonitor results

5.1.1 Marker MoM

Automonitor displays a tile for each maternal serum and ultrasound marker (Figure 70). When the median MoM value is outside the 95% confidence interval for the marker it will be indicated as an issue – an item which requires your attention. When the median weight is 5kg different (or 10 pounds different if the weight units chosen are pounds) from the weight for which the MoM weight adjustment factor is 1.0 (see section 3.2.1.2) it will also be indicated as an issue. Separate issues will be shown when appropriate for each ethnic group for whom a direct median equation has been specified (see section 3.1.3). If more than one issue is indicated for a marker then the issues are shown by hovering over the tile.

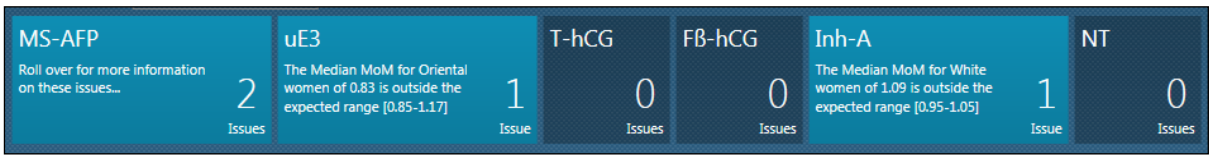


Figure 70: Automonitor - Markers

5.1.2 Report summary

The **Report summary** section (Figure 71) gives the number and percentage of reports which are screen positive, screen negative and uninterpretable for Down's syndrome screening for all the tests carried out.

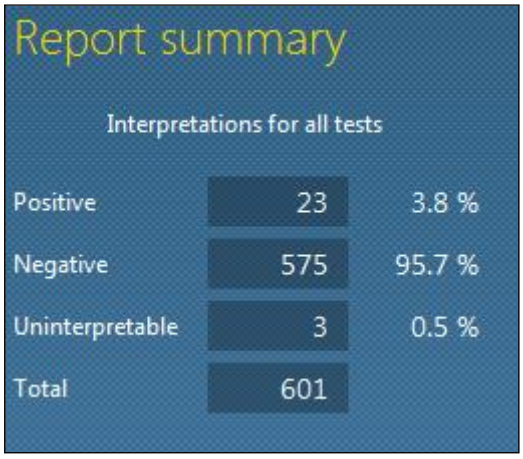


Figure 71: Automonitor - Report Summary

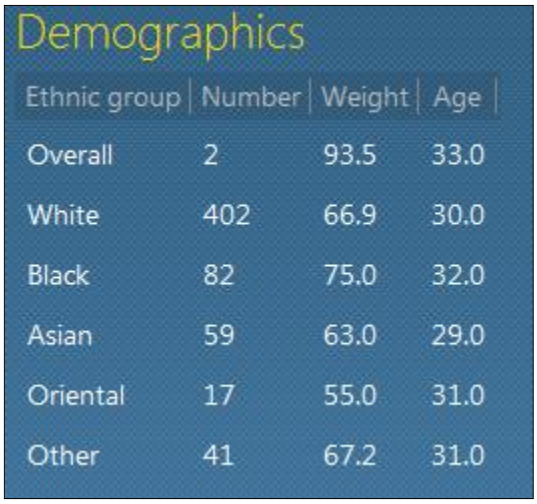
5.1.3 Test specific summary

The **Test specific** summary section (Figure 72) allows you to select one of the marker combinations used to calculate screening performance tables (See Section 5.11). It shows a summary of reports which used this marker combination (Report Summary) and the expected screening performance derived from the maternal age distribution of the population who were screened using this marker combination (Expected Performance). This allows you to easily compare the observed positive rate with the expected false positive rate in your screening programme.

Figure 72: Automonitor - Test Specific Summary

5.1.4 Demographics

Demographics (Figure 73) shows, for each ethnic group, the number of women screened, their median weight and median age.



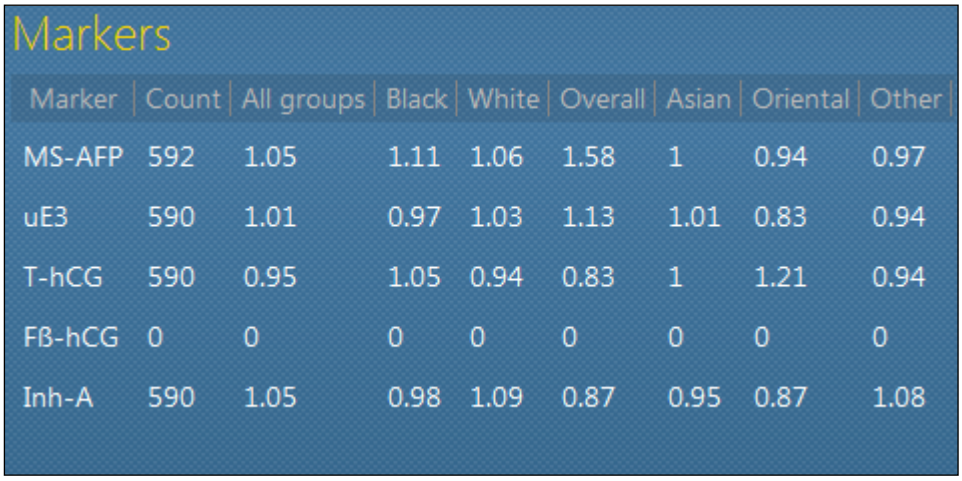
Demographics

Ethnic group	Number	Weight	Age
Overall	2	93.5	33.0
White	402	66.9	30.0
Black	82	75.0	32.0
Asian	59	63.0	29.0
Oriental	17	55.0	31.0
Other	41	67.2	31.0

Figure 73: Automonitor - Demographics

5.1.5 Markers

Markers (Figure 74) shows for each serum marker, the number of measurements taken, and the median MoM for all groups and each ethnic group separately.



Markers

Marker	Count	All groups	Black	White	Overall	Asian	Oriental	Other
MS-AFP	592	1.05	1.11	1.06	1.58	1	0.94	0.97
uE3	590	1.01	0.97	1.03	1.13	1.01	0.83	0.94
T-hCG	590	0.95	1.05	0.94	0.83	1	1.21	0.94
Fß-hCG	0	0	0	0	0	0	0	0
Inh-A	590	1.05	0.98	1.09	0.87	0.95	0.87	1.08

Figure 74: Automonitor - Markers

5.1.6 Nuchal Translucency

Nuchal Translucency (Figure 75) shows for all sonographers and for each sonographer the number of measurements and the median NT MoM.

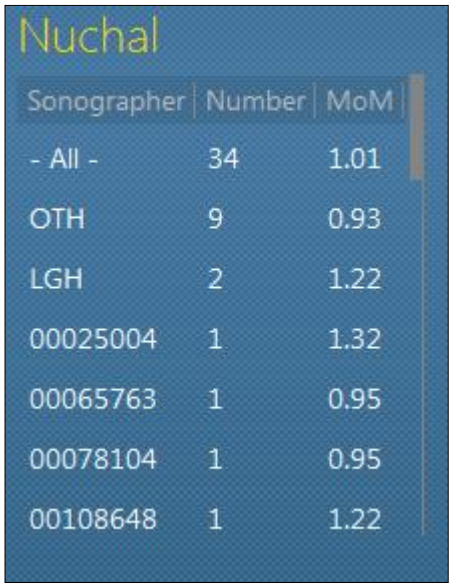


Figure 75: Automonitor - Nuchal Translucency

5.2 Analyse-it

The **Analyse-it** option provides a powerful and flexible facility for users to analyze their MS and AF data. It can be used to export data to a text file or directly to a Microsoft ® Excel ® spreadsheet. *Appendix* G *Import, Export, Data transfer and Analyze-it formats* gives the meaning and format of the fields exported using **Analyse-it**.

When the option is selected, a screen similar to Figure 76 is shown. If you have already prepared an **Analyse-it** query it can be selected from the list in the left hand side of the screen. To create a new MS or AF query select either the **New MS Query** and **New AF Query** buttons**.** Press the **Save Query** to save a new query. To delete a selected query press the **Delete query** button.

Once selected, the query can be run or modified. Four tabs are available: **Options**, **Output**, **Criteria** and **Ordering**. The **Options** tab (Section 5.2.1) is used to test and run the query and specify the type of results file and filename, **Output** (Section 5.2.2) to specify the fields to export, **Criteria** (Section 5.2.3) to specify the criteria used for selecting the fields and **Ordering** (Section 5.2.4) how the results are ordered.

Sections 5.2.2 to 5.2.5 illustrate the features of **Analyse-it** by means of a worked example. The query will return a dataset from **αlpha** that can be used to examine the median gestational age of all women screened with the Integrated test in a certain date range.

5.2.1 Options

The **Options** tab allows you to select results whether the results are written to an Excel ® spreadsheet, a comma or tab separated text file or into an XML format. The results filename is specified in the Output File Path text entry box. To test the query, press the **Test Query** button. This will show the number of rows of data it will return. To run the query and write the data to the type of file and filename specified press the **Run Query** button. (See Section 5.2.5)

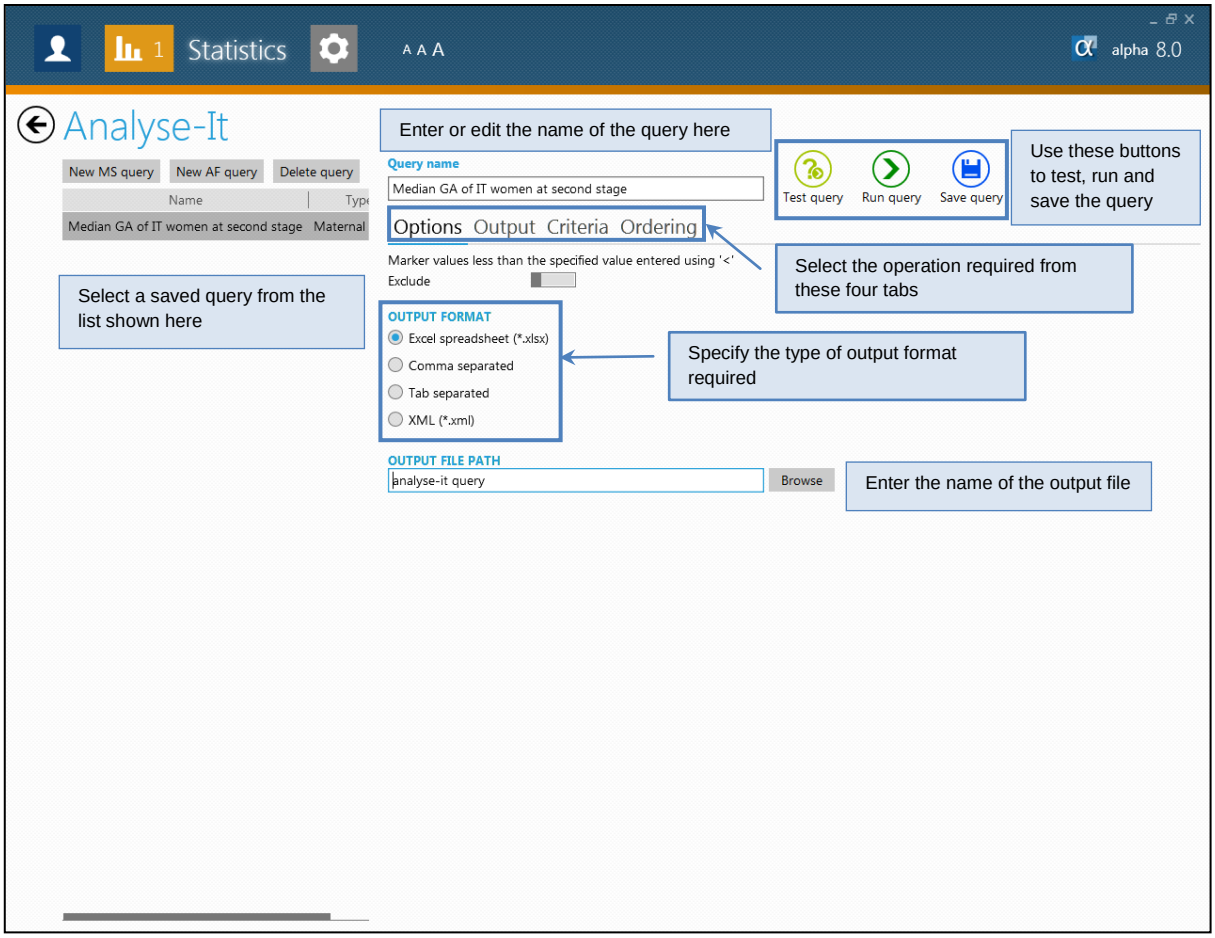


Figure 76: Analyse-it Options

5.2.2 Output

The **Output** tab specifies the database fields to include in the output (See Figure 77). The left hand column shows the database fields which can be selected and the right hand column the fields in the selected query. Click and drag the fields between the two columns to add and remove them from the query.

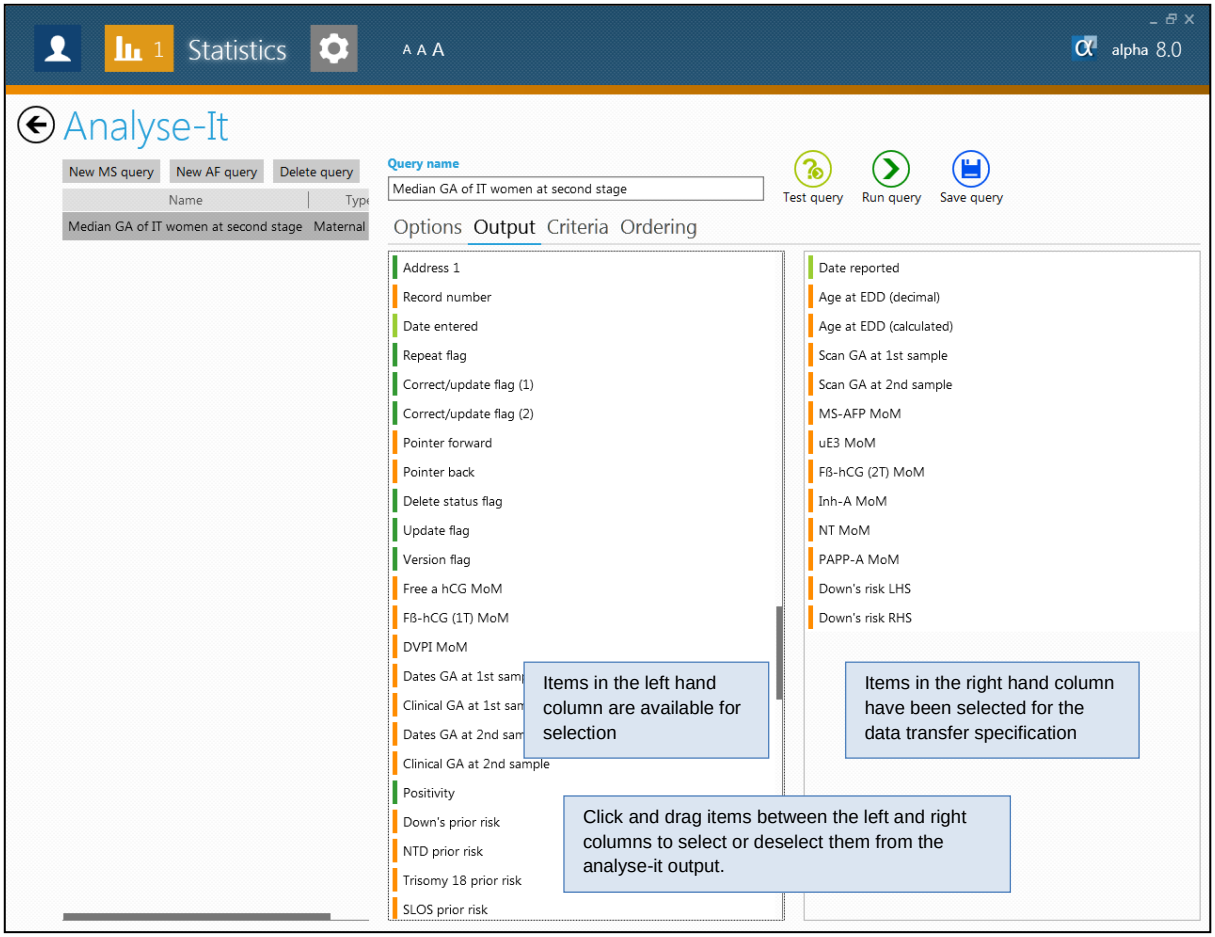


Figure 77: Analyse-it Output

5.2.3 Criteria

The **Criteria** tab shows the criteria used to select the records in the results. Before any criteria have been added a screen similar to that in Figure 78 will be shown when tab is selected.

An **Analyse-it** query consists of a number of criteria. A criterion is a rule which needs to be true for the record to appear in the results. The criterion consists of a left hand side, an operator and a right hand side. The left hand side is one of the **αlpha** database field names, the operator one of the terms in Table 10 and the right hand side a constant such a text string, number or date. The following are examples of criteria:

MS-AFP MoM > 2.0	True if the MS-AFP MoM value is greater than 2.0
Date Reported <= 01/01/2013	True if the report date is on or earlier than 1 January 2013.

Criteria can be combined with the logical AND and OR operators to create complex queries. You can enter NULL in the right hand side to denote an empty database field.

Table 10: Analyze-it operators

Operator	Meaning
=	Equals
<>	Not equal to
>	Greater than
≥	Greater than or equal to
<	Less than
≤	Less than or equal to
Like	Searches for a specified pattern. For example JON% matches all fields starting with JON
In	Matches a field to one of a series of values. Specify the values to match on as a series of values separated by commas.

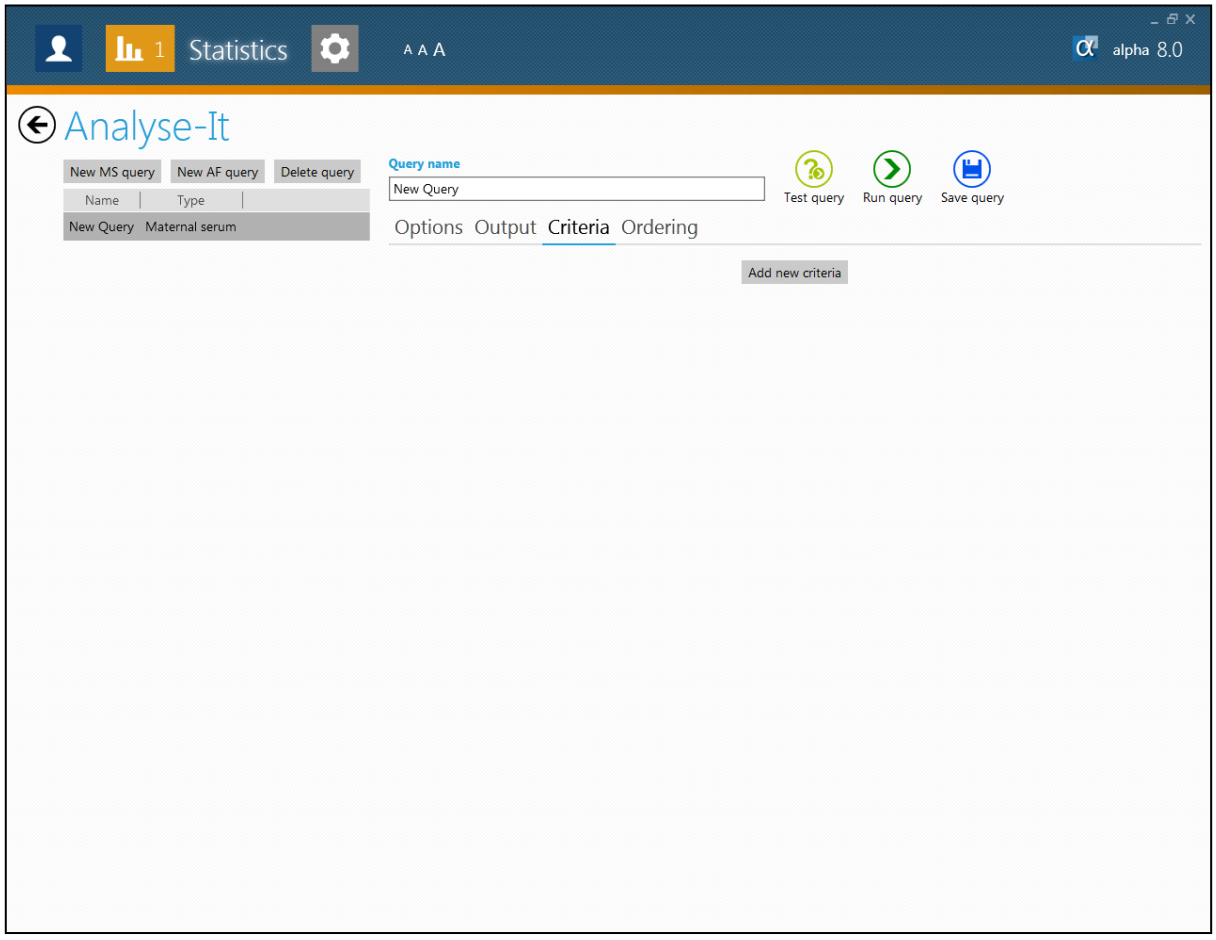


Figure 78: Analyse-it Criteria

Press the **Add Criteria** button to add a new criterion to the **Analyse-it** query. The left hand side of the criteria is selected from the drop down list containing the field names in the **αlpha** database (See Figure 79), the operator from the drop down list containing the available operators and the right hand side entered into the text box. Press the **Add Criteria** button again to add further criteria to build up the whole query (See Figure 80).

The **αlpha** database fields specified in the **Output** tab (Section 5.2.2) are included in the results if the criteria specified in Figure 80 are all satisfied. Table 11 provides an explanation of the criteria used in this example.

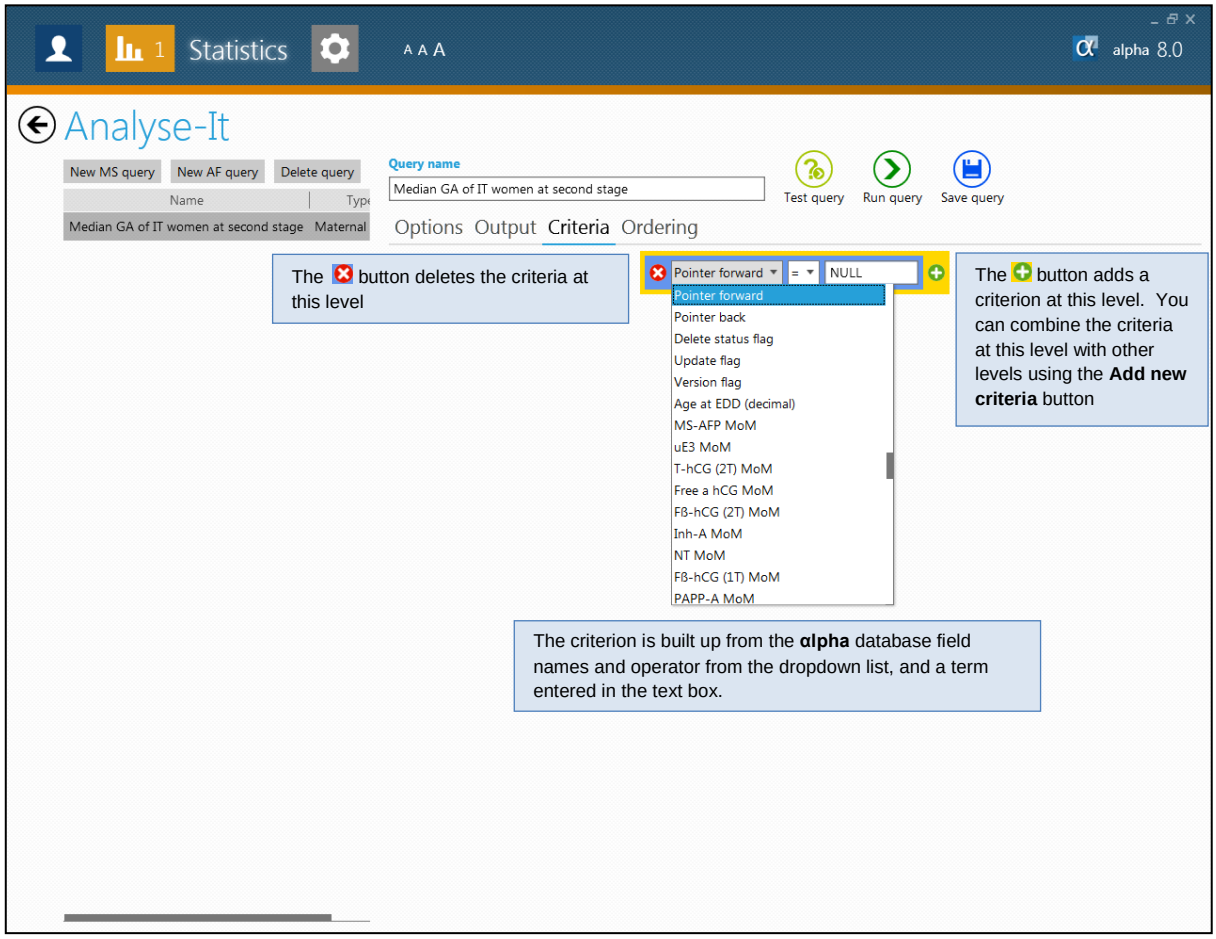


Figure 79: Analyse-it criteria: entering a criteria

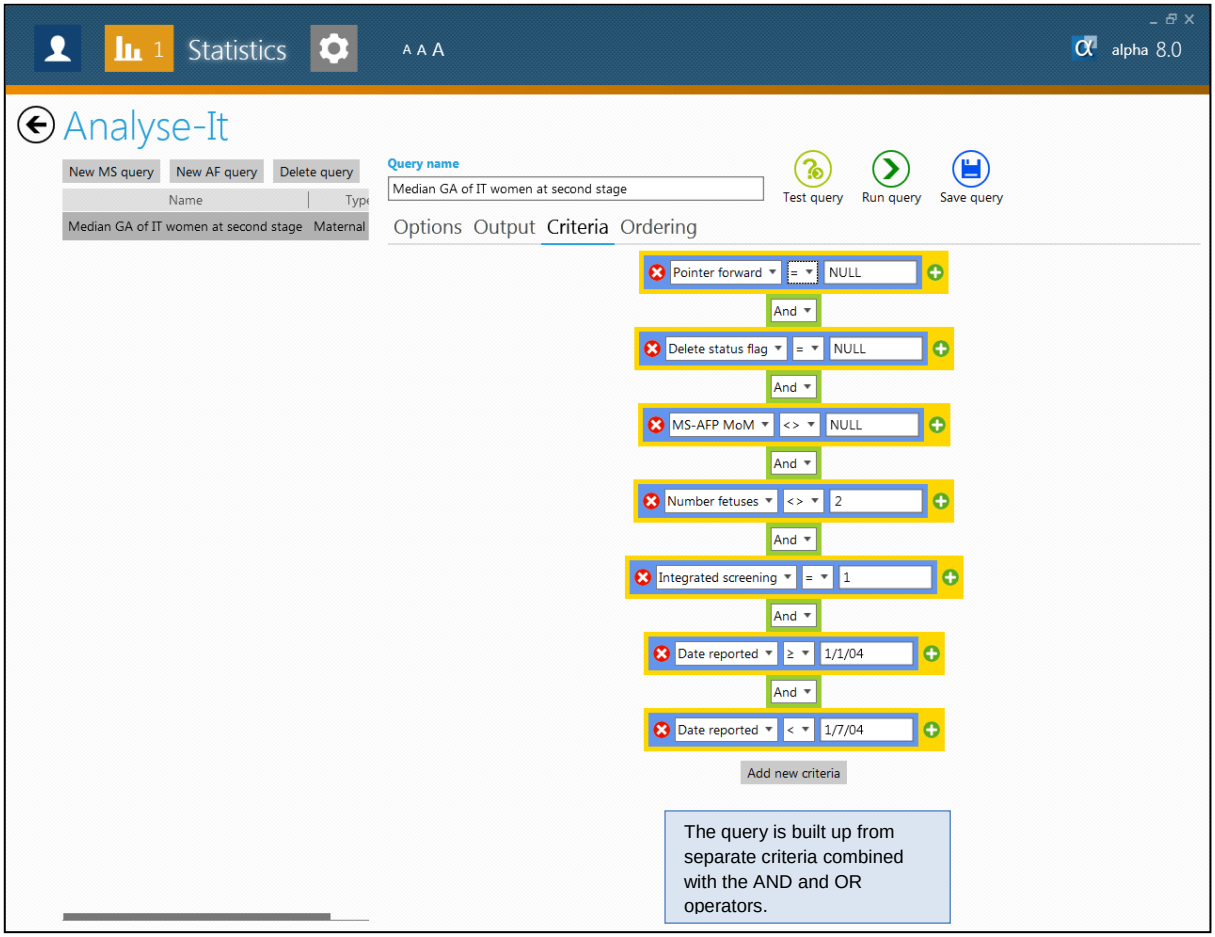


Figure 80: Analyse-it Complete query

Table 11: Explanation of criteria used in Analyse-it example

Criteria	Meaning
PointerForward = NULL	Do not include corrected records
Delete Status Flag = NULL	Do not include deleted records
MS-AFP MoM <> NULL	Include records where the MS-AFP MoM is specified
Number of fetuses <> 2	Include records where the number of fetuses is not equal to 2
Integrated Screening = 1	Include records when the Integrated test was performed
Date reported ≥ 1/1/04	Include records where the report date was on or later than 1 January 2004
Date reported < 1/7/04	Include records where the report date was before 1 July 2004

5.2.4 Ordering

The order in which the results are exported are specified on the **Ordering** tab (See Figure 81). In this example reports will be ordered using the **αlpha** report date field.

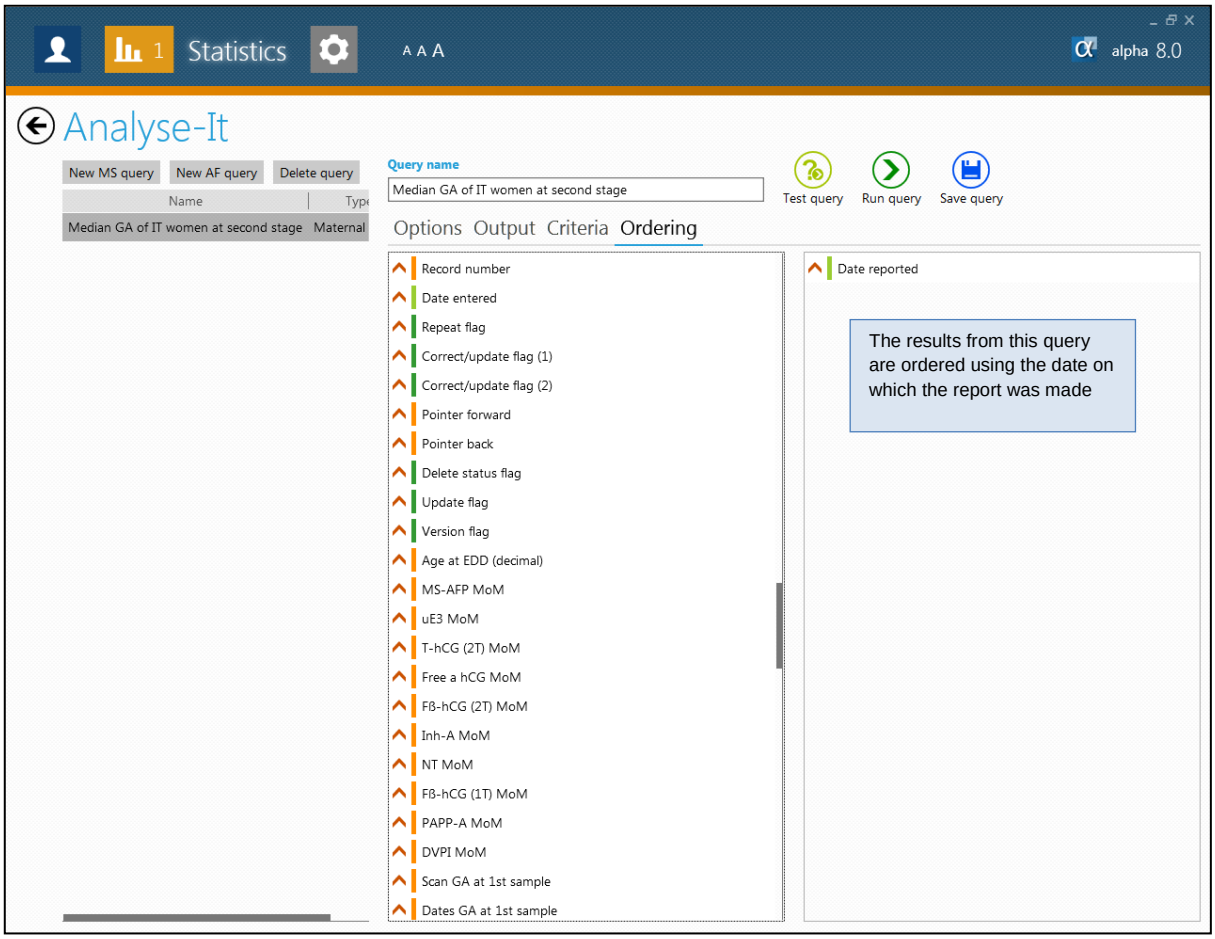
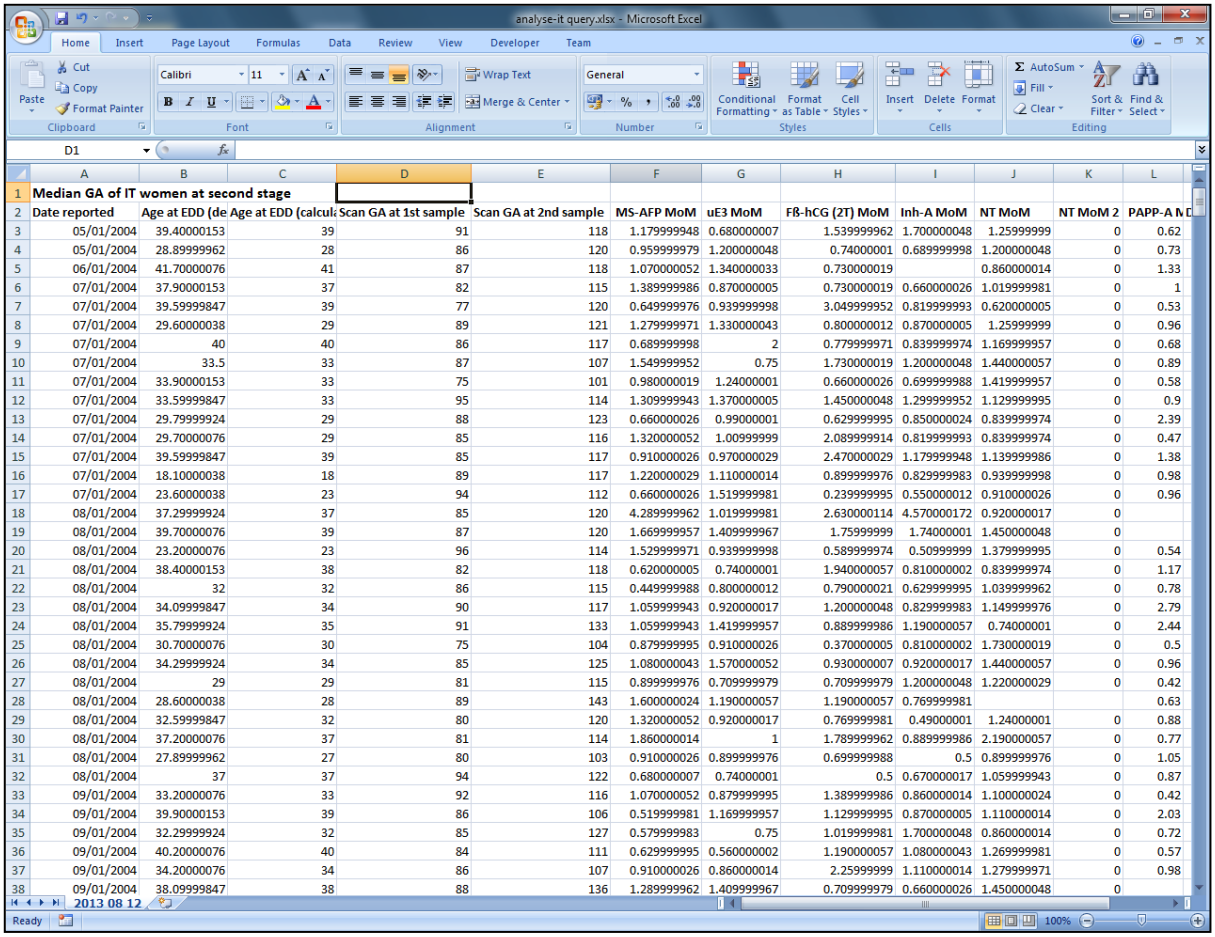


Figure 81: Analyse-it Ordering

5.2.5 Query results

To test the query, press the **Test Query** button. This will show the number of rows of data it will return. To run the query and write the data to the type of file and filename specified press the **Run Query** button.

Selected results from the query prepared in the previous sections are shown exported to an Excel file (Figure 82) and to XML format (Figure 83).



analyse-it query.xlsx - Microsoft Excel

	A	B	C	D	E	F	G	H	I	J	K	L
1	Median GA of IT women at second stage											
2	Date reported	Age at EDD (de	Age at EDD (calcul	Scan GA at 1st sample	Scan GA at 2nd sample	MS-AFP MoM	uE3 MoM	Fß-hCG (2T) MoM	Inh-A MoM	NT MoM	NT MoM 2	PAPP-A M
3	05/01/2004	39.40000153	39	91	118	1.179999948	0.680000007	1.539999962	1.700000048	1.25999999	0	0.62
4	05/01/2004	28.89999962	28	86	120	0.959999979	1.200000048	0.74000001	0.689999998	1.200000048	0	0.73
5	06/01/2004	41.70000076	41	87	118	1.070000052	1.340000033	0.730000019		0.860000014	0	1.33
6	07/01/2004	37.90000153	37	82	115	1.389999986	0.870000005	0.730000019	0.660000026	1.019999981	0	1
7	07/01/2004	39.59999847	39	77	120	0.649999976	0.939999998	3.049999952	0.819999993	0.620000005	0	0.53
8	07/01/2004	29.60000038	29	89	121	1.279999971	1.330000043	0.800000012	0.870000005	1.25999999	0	0.96
9	07/01/2004	40	40	86	117	0.689999998	2	0.779999971	0.839999974	1.169999957	0	0.68
10	07/01/2004	33.5	33	87	107	1.549999952	0.75	1.730000019	1.200000048	1.440000057	0	0.89
11	07/01/2004	33.90000153	33	75	101	0.980000019	1.24000001	0.660000026	0.699999988	1.419999957	0	0.58
12	07/01/2004	33.59999847	33	95	114	1.309999943	1.370000005	1.450000048	1.299999952	1.129999995	0	0.9
13	07/01/2004	29.79999924	29	88	123	0.660000026	0.99000001	0.629999995	0.850000024	0.839999974	0	2.39
14	07/01/2004	29.70000076	29	85	116	1.320000052	1.00999999	2.089999914	0.819999993	0.839999974	0	0.47
15	07/01/2004	39.59999847	39	85	117	0.910000026	0.970000029	2.470000029	1.179999948	1.139999986	0	1.38
16	07/01/2004	18.10000038	18	89	117	1.220000029	1.110000014	0.899999976	0.829999983	0.939999998	0	0.98
17	07/01/2004	23.60000038	23	94	112	0.660000026	1.519999981	0.239999995	0.550000012	0.910000026	0	0.96
18	08/01/2004	37.29999924	37	85	120	4.289999962	1.019999981	2.630000114	4.570000172	0.920000017	0	
19	08/01/2004	39.70000076	39	87	120	1.669999957	1.409999967	1.75999999	1.74000001	1.450000048	0	
20	08/01/2004	23.20000076	23	96	114	1.529999971	0.939999998	0.589999974	0.50999999	1.379999995	0	0.54
21	08/01/2004	38.40000153	38	82	118	0.620000005	0.74000001	1.940000057	0.810000002	0.839999974	0	1.17
22	08/01/2004	32	32	86	115	0.449999988	0.800000012	0.790000021	0.629999995	1.039999962	0	0.78
23	08/01/2004	34.09999847	34	90	117	1.059999943	0.920000017	1.200000048	0.829999983	1.149999976	0	2.79
24	08/01/2004	35.79999924	35	91	133	1.059999943	1.419999957	0.889999986	1.190000057	0.74000001	0	2.44
25	08/01/2004	30.70000076	30	75	104	0.879999995	0.910000026	0.370000005	0.810000002	1.730000019	0	0.5
26	08/01/2004	34.29999924	34	85	125	1.080000043	1.570000052	0.930000007	0.920000017	1.440000057	0	0.96
27	08/01/2004	29	29	81	115	0.899999976	0.709999979	0.709999979	1.200000048	1.220000029	0	0.42
28	08/01/2004	28.60000038	28	89	143	1.600000024	1.190000057	1.190000057	0.769999981			0.63
29	08/01/2004	32.59999847	32	80	120	1.320000052	0.920000017	0.769999981	0.49000001	1.24000001	0	0.88
30	08/01/2004	37.20000076	37	81	114	1.860000014	1	1.789999962	0.889999986	2.190000057	0	0.77
31	08/01/2004	27.89999962	27	80	103	0.910000026	0.899999976	0.699999988	0.5	0.899999976	0	1.05
32	08/01/2004	37	37	94	122	0.680000007	0.74000001	0.5	0.670000017	1.059999943	0	0.87
33	09/01/2004	33.20000076	33	92	116	1.070000052	0.879999995	1.389999986	0.860000014	1.100000024	0	0.42
34	09/01/2004	39.90000153	39	86	106	0.519999981	1.169999957	1.129999995	0.870000005	1.110000014	0	2.03
35	09/01/2004	32.29999924	32	85	127	0.579999983	0.75	1.019999981	1.700000048	0.860000014	0	0.72
36	09/01/2004	40.20000076	40	84	111	0.629999995	0.560000002	1.190000057	1.080000043	1.269999981	0	0.57
37	09/01/2004	34.20000076	34	86	107	0.910000026	0.860000014	2.25999999	1.110000014	1.279999971	0	0.98
38	09/01/2004	38.09999847	38	88	136	1.289999962	1.409999967	0.709999979	0.660000026	1.450000048	0	

2013 08 12

Ready

Figure 82: Analyse-it Results in Excel ®

```
<record>
    <ReportDate>05/01/2004 00:00:00</ReportDate>
    <EDDAge>39.4</EDDAge>
    <IntegerEDDAge>39</IntegerEDDAge>
    <ScanGA1>91</ScanGA1>
    <ScanGA2>118</ScanGA2>
    <M1MoM1>1.18</M1MoM1>
    <M2MoM1>0.68</M2MoM1>
    <M5MoM1>1.54</M5MoM1>
    <M6MoM1>1.7</M6MoM1>
    <M7MoM1>1.26</M7MoM1>
    <M7MoM2>0</M7MoM2>
    <M7MoM2>0</M7MoM2>
    <M9MoM1>0.62</M9MoM1>
    <D1PostL>1</D1PostL>
    <D1PostR>440</D1PostR>
</record>
```

Figure 83: Analyse-it XML format

5.3 Data transfer

The **Data Transfer** option allows selected fields from the MS or AF database to be exported to another software program. Section 3.5 describes how to specify or change the fields to be exported and how to store them in a data transfer specification.

When the option is selected, a screen similar to Figure 84 is shown. The data transfer specification description can be selected from a drop down and the filename in which the results are to be stored specified. You can select whether reports are to be exported from the MS or AF database and which tests (first trimester, second trimester, integrated, sequential or all tests) should be included. You can also select the date range for the report and screening reports associated with selected report addresses, doctors or sonographers be included or excluded from the analysis (See Section 5.13.2).

Press the **Transfer** to start the transfer. When the transfer is complete, αlpha asks if you want to open the data transfer file.

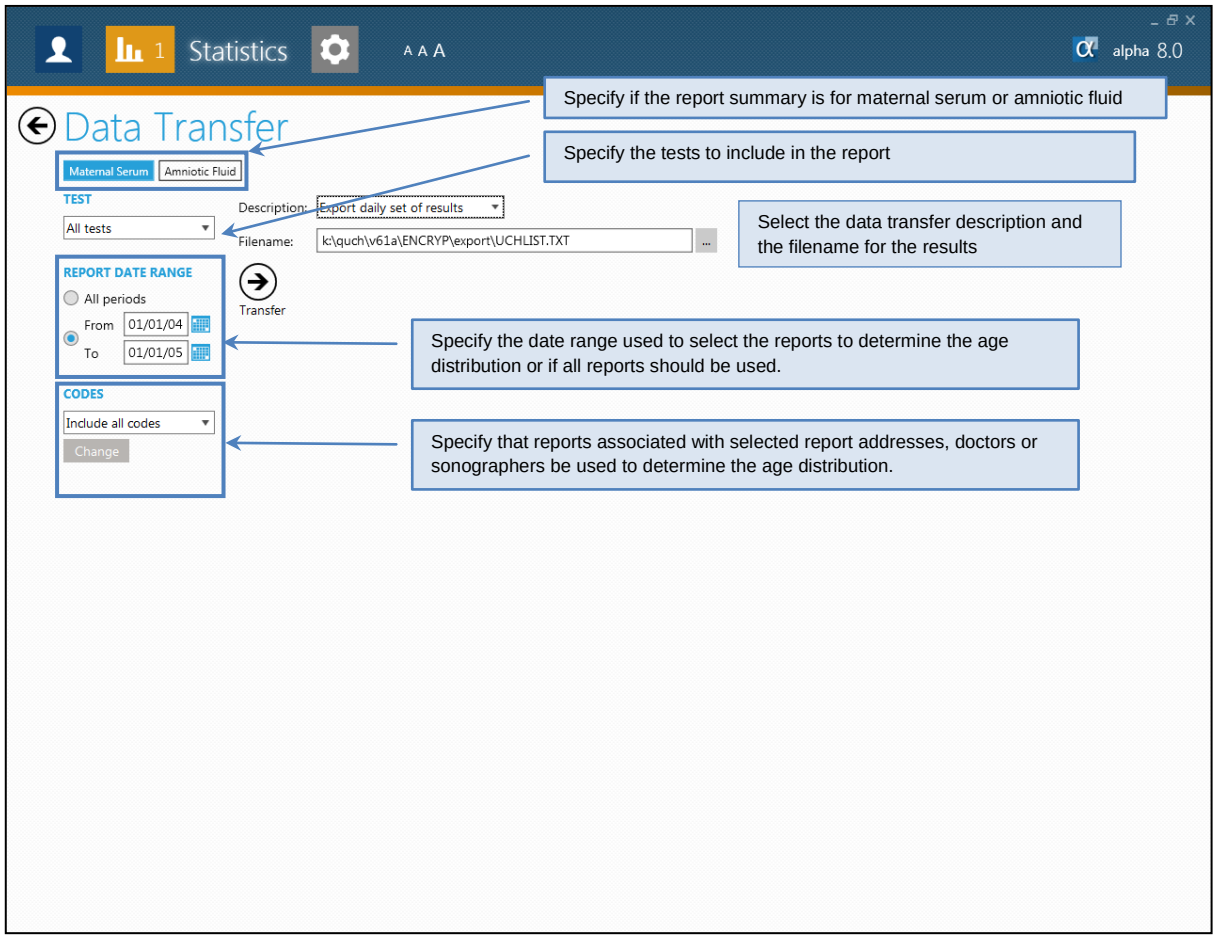


Figure 84: Data Transfer

5.4 Median Analysis

The **Median Analysis** option provides a graphical and tabular summary of the reported median MoM values for the screening markers and for AF-AFP, by day, week, month or quarter during the requested time period. Women of selected ethnic groups can be included in the analysis, and reports associated with selected report addresses, doctors or sonographers be included or excluded from the analysis. Smokers may be included or excluded from this analysis.

This option is useful for monitoring long term trends and short term fluctuations in the marker levels.

Restricting the summary to specified sonographers can be useful in monitoring differences in NT measurements made by different sonographers. If differences are identified, you may wish to consider specifying sonographer-specific medians for NT measurement. (See Section 5.6)

When the **Median Analysis** option is first selected the screen Figure 85 in is shown. Once the options have been selected and the **Refresh** button pressed a screen similar to that in Figure 86 showing a graphical summary of the reported median MoM value.

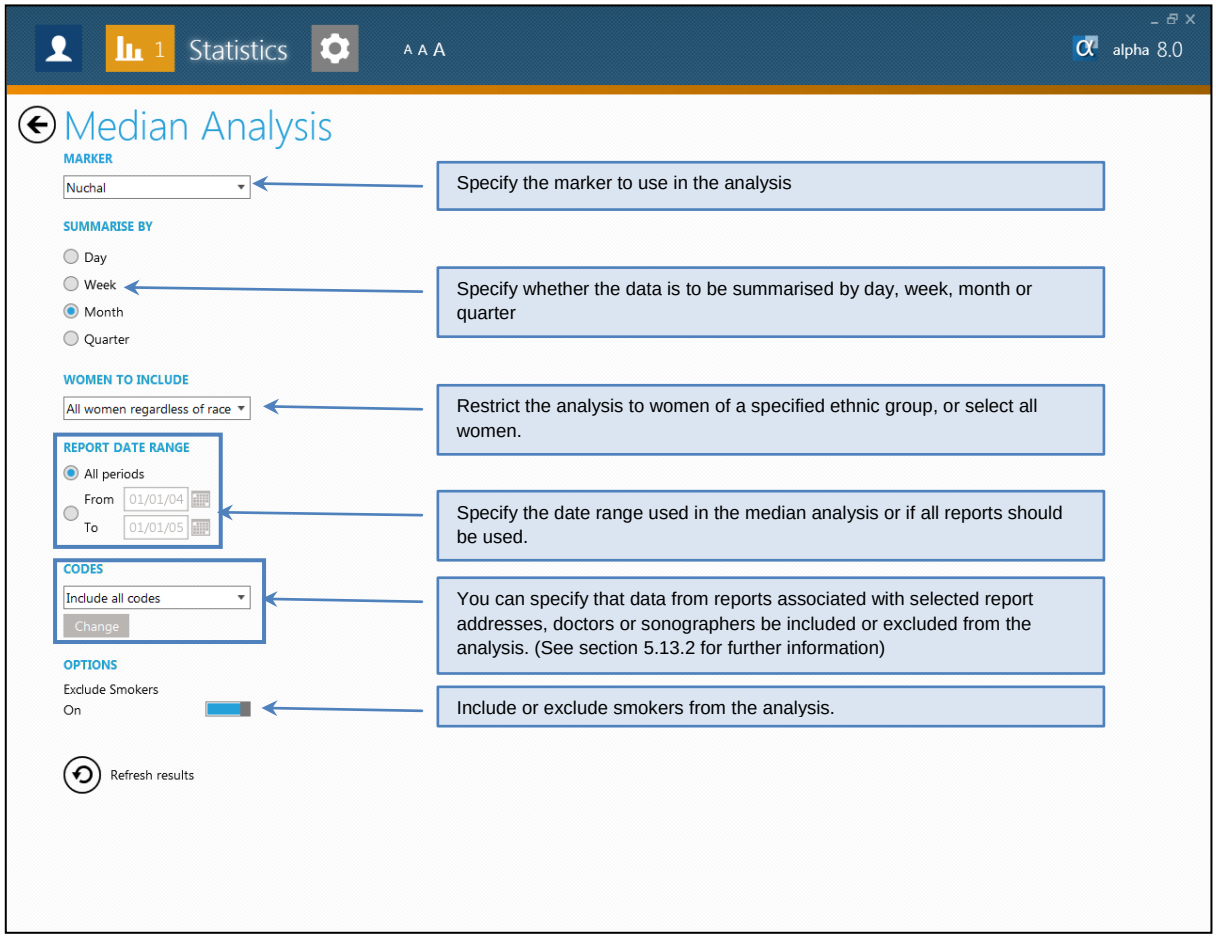


Figure 85: Options in Median Analysis

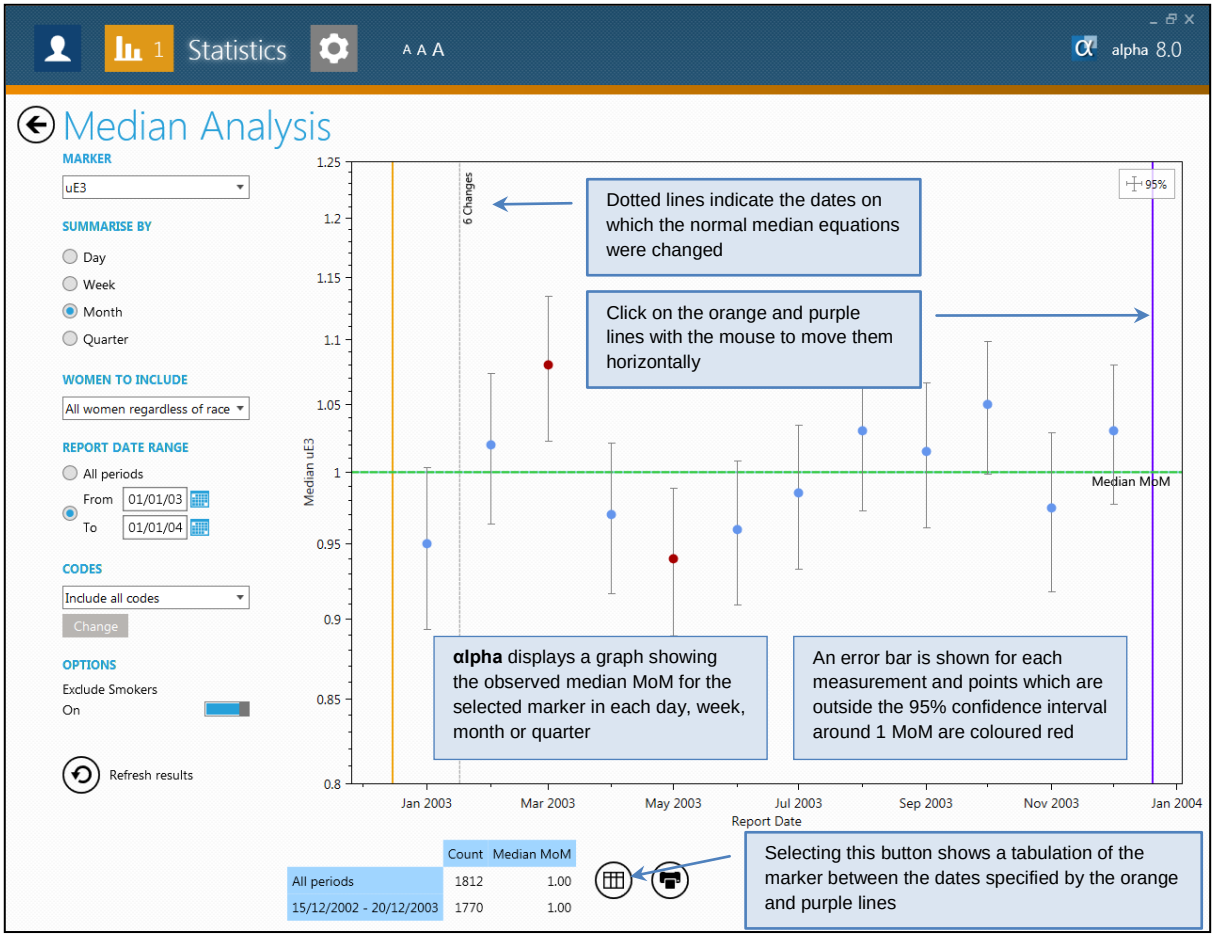


Figure 86: Median Analysis for uE_3

The **Median Analysis** graph can be moved horizontally and vertically by moving the mouse with the right button held down. Moving the mouse wheel will zoom in and out of the graph. Moving the mouse with the mouse wheel held down will select an area to zoom into when the mouse wheel is released.

Pressing the **Tabulated Selected Period** button shows a tabulation (see Section 5.2) of the selected marker for the date range specified by the position of the orange and purple lines.

Press the **Print** button for a printed copy of the **Median Analysis.**

Patterns of markers which are consistently high or low may indicate that the current estimates of the normal median are incorrect and need to be changed. See Section 5.9.4 for further information on monitoring and changing the medians. The median analysis screen provides options for printing the report and shows where coefficient changes took place.

5.5 Missing information

The **Missing Information** option provides a breakdown by doctor or report address of the proportion of reports for which information normally entered into the data entry screen is missing for a specified date range. The table is useful for determining which doctors or centres routinely provide, for example, maternal weight and scan information.

When the **Missing Information** option is selected a screen similar to that in Figure 87 is shown. This shows that 6136 tests were carried out in the specified period and that 15.19% of them were missing maternal weight. These results are broken down by address code showing that, for example 14 tests (14.3%) were missing maternal weight in address code 102.

Any field in the **αlpha** data entry screen can be included in the report of missing information. To include another field, select it from the drop down list and press the **Add** button. An example of this is shown in Figure 88 which shows that 14.6% of reports were missing LMP information. Fields can be combined to show to show reports which were missing more than one piece of information. For example, in Figure 88 pressing the **Add** button on the right of the screen will include another column showing reports which were missing both LMP and Ethnic Origin. Pressing the ⊖ button next to a column will remove it from the report.

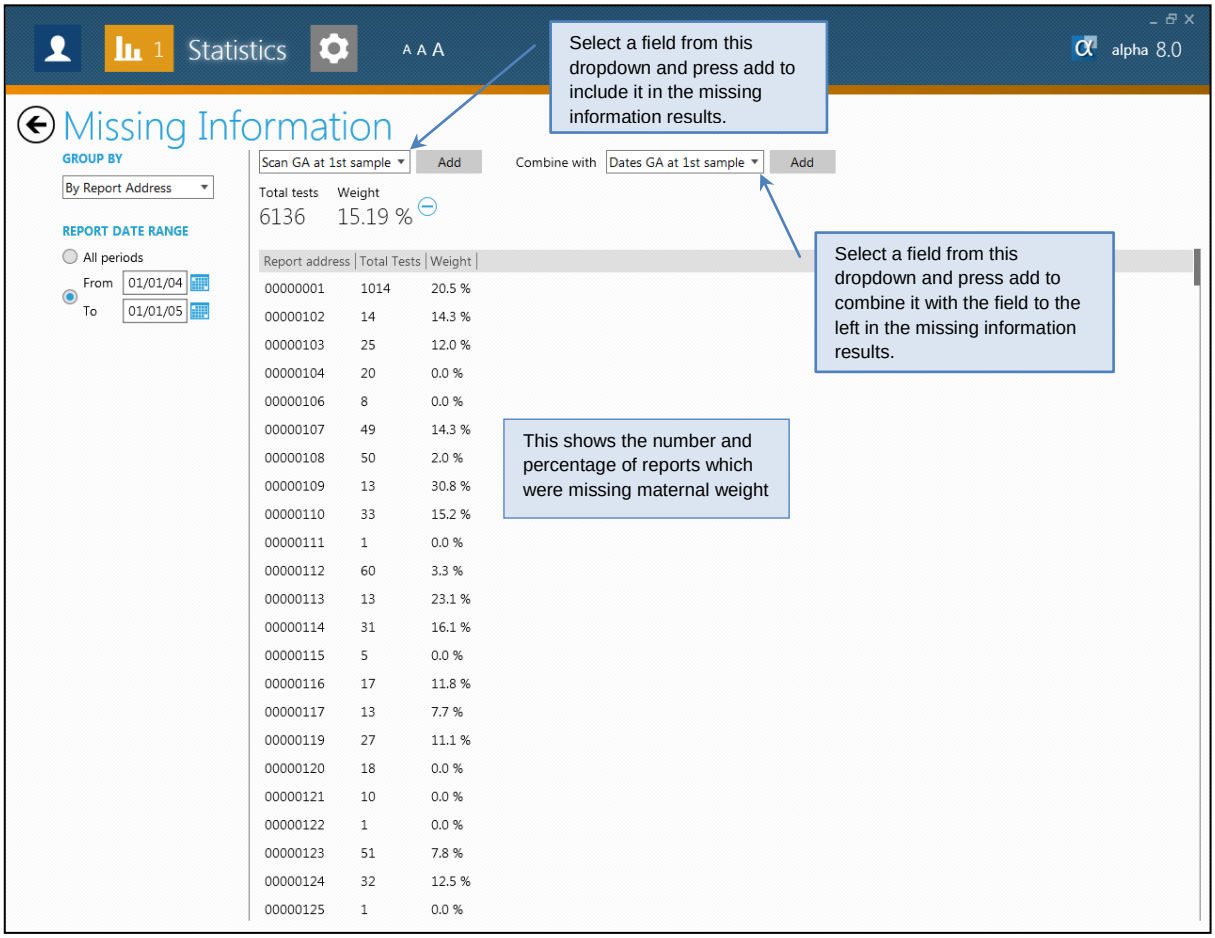


Figure 87: Missing information

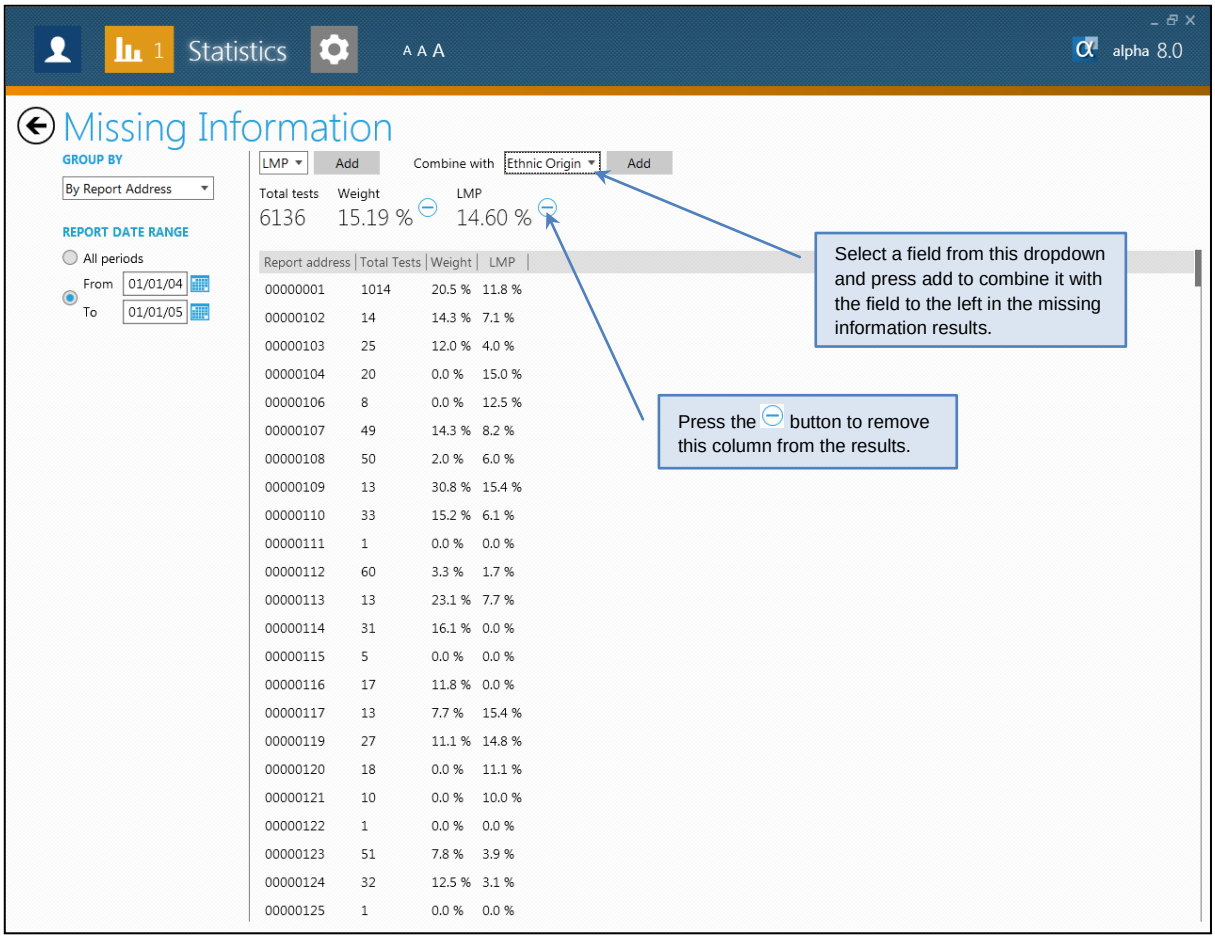


Figure 88: Missing information - adding additional fields

5.6 Nuchal translucency monitor

The **Nuchal Translucency Monitor** feature in **αlpha** provides a facility for quick and easy monitoring of sonographer or site specific nuchal translucency medians. This will be useful for users who need to regularly monitor NT medians for a large number of different sonographers. When the NT monitor option is selected, a screen similar to that in Figure 89 is shown.

For each selected sonographer or address code a graph showing the NT measurements taken and fitted regression equation is displayed for the selected date range. The number of measurements, median MoM, standard deviation and increase per week is also displayed. The graph can be plotted with a linear or logarithmic Y axis. The axis range will scale automatically to the measured data, but to suppress this behaviour (for example to facilitate comparisons between different sonographers) select **Fixed Axis Range** on. The graph can be printed by pressing the button. The **Analyse Codes** button prepares a report showing the number of measurements, median MoM, standard deviation and increase per week for all sonographers or address code for the time period selected. The **Audit Code** button prepares a report for the selected sonographer or address code showing the number of measurements, median MoM, standard deviation and increase per week for the two preceeding years.

Figure 89: Nuchal Translucency Monitor

5.7 Outcome

αlpha outcome may be used to enter and store information on the outcome of pregnancies and on any diagnostic procedures carried out, among screened women. The presence or absence of neural tube defects, Down's syndrome and other birth defects can be recorded, using the 10th edition of the international classification of diseases (ICD codes).

A range of screening audit facilities provides statistical information useful in monitoring screening performance.

Each pregnancy screened using the **αlpha** software can have an outcome associated with it, containing all data on the outcome of the foetuses. This data can then be used to analyse the screening performance using the various sections in **αlpha** Outcome.

5.7.1 Outcome Sections

The various features of Outcome are accessed from a menu to the left of the screen (Figure 90).

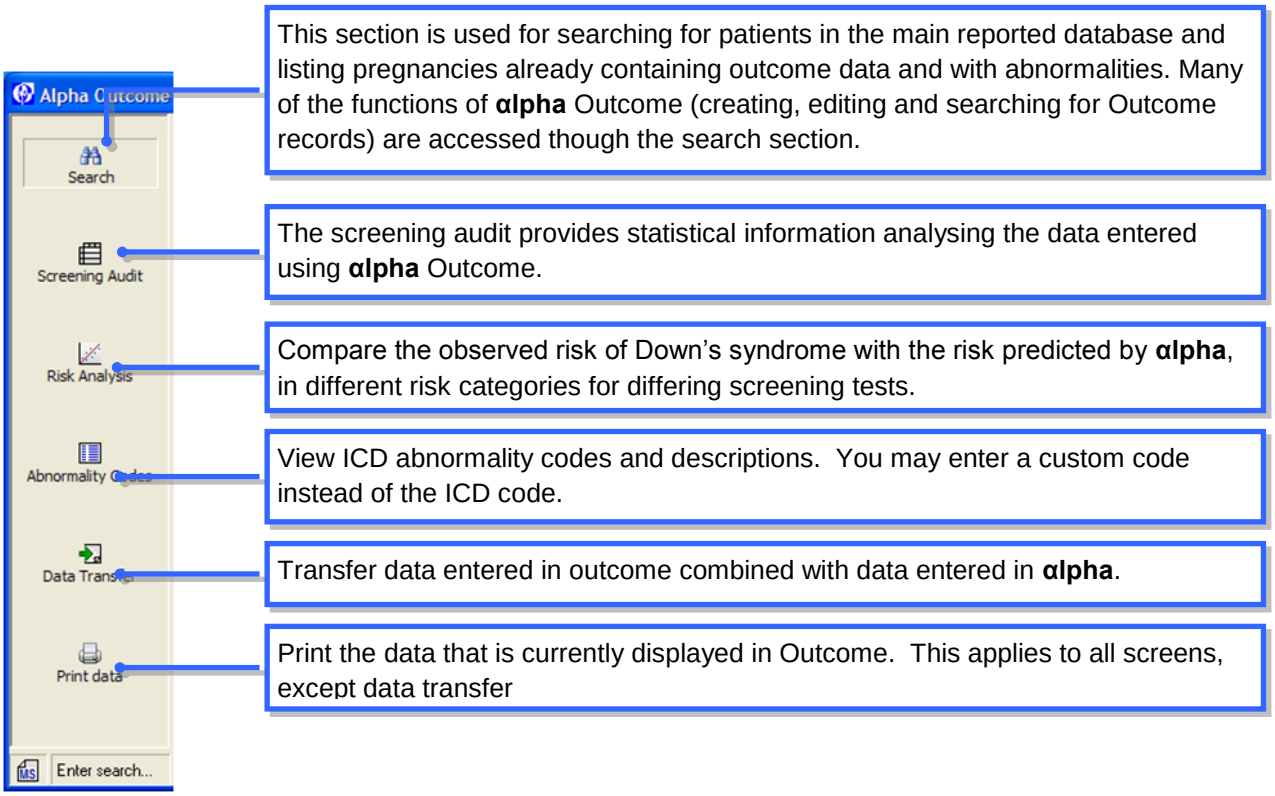


Figure 90: Outcome sections

αlpha outcomes can be entered for both Maternal Serum (MS) and Amniotic Fluid (AF) screening programmes. The symbol  in the bottom left of the outcome screen shows the screening programme outcome is currently using. Risk analysis is not available in AF outcome analysis.

5.7.2 Search

When **αlpha** Outcome first starts the first screen to appear is the search screen as shown in Figure 91.

To return to the Search section click on the 

icon on the side bar.

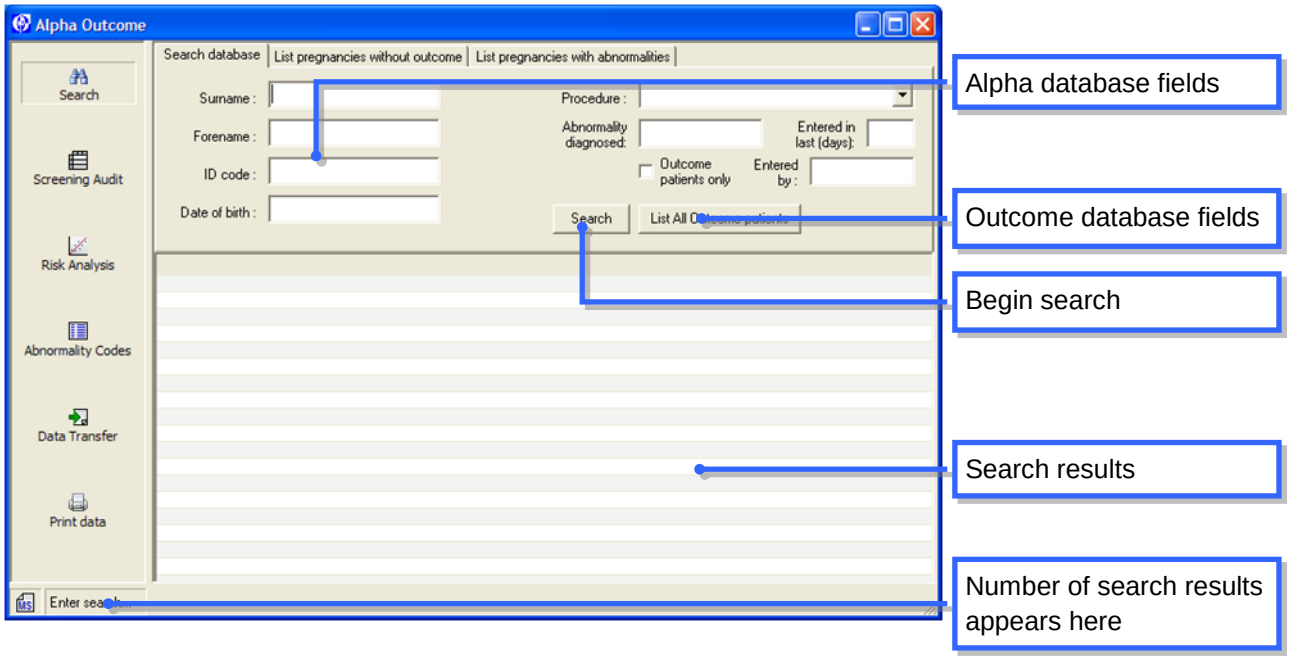


Figure 91: Outcome search

The **Search** section consists of three tabs for searching the **αlpha** database and listing pregnancies with different filters.

Double-clicking on any patient in any of the open tabs will open their outcome details, or allow the user to create new outcome details for that pregnancy.

5.7.2.1 Search Database

Search database enables the user to list all reported patients in the **αlpha** database and enter outcome data or view previously entered data for those patients, filtered on the patient details or by some outcome details. The Search database is the main section used to select the patient for the creating and editing of outcome data (see Section 5.7.3)

5.7.2.2 List Pregnancies without Outcome

This tab is used to list all pregnancies for which an outcome has not been entered (See Figure 92). This can be filtered by the screening result, report date or by doctor and address codes.

Clicking on the ‘Change’ button next to the doctor and address code options, allows the selected doctors and address codes to be changed.

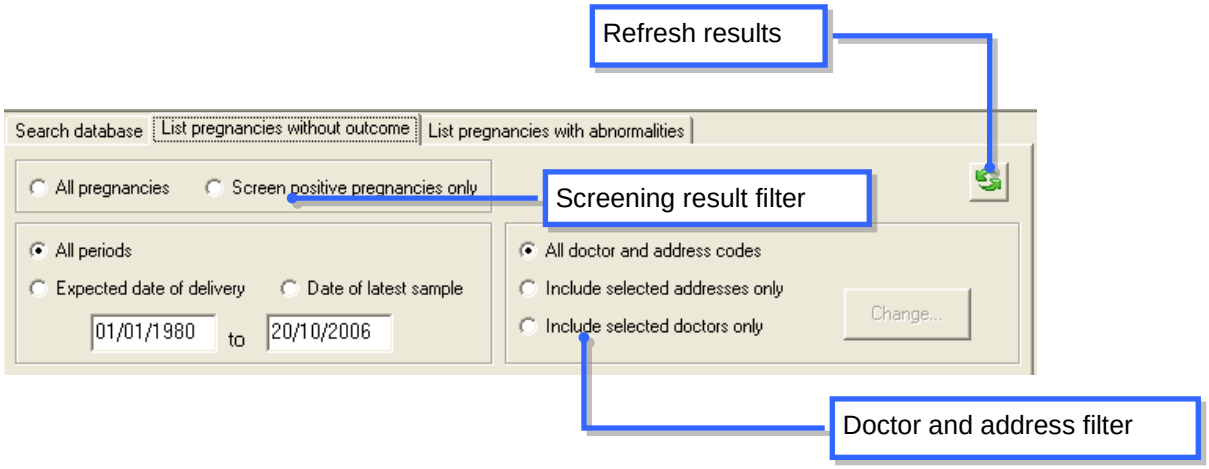


Figure 92: Pregnancies without Outcome

Once this list has been compiled, it can be printed in by clicking the print button on the side bar. The user can either choose to simply print the list or an Outcome request sheet can be created containing details of the patient and spaces for details on the outcome to be filled in.

5.7.2.3 List Pregnancies with Abnormalities

This tab is used to list all pregnancies for which an outcome containing an abnormality has been entered. This can be filtered by the report date or by doctor and address codes.

To **list pregnancies with abnormalities** requires the selection of up to seven different abnormality codes. For example in the case of Down’s syndrome, this allows for all associated codes to be listed in a single screen (See Figure 93).

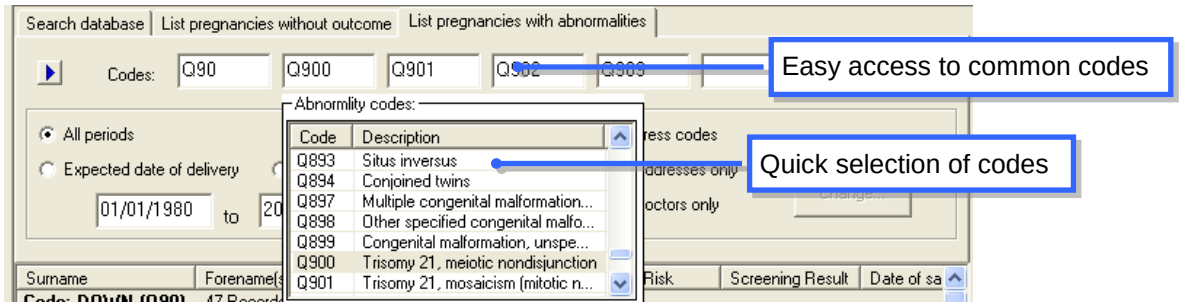


Figure 93: Outcome : List pregnancies with abnormalities

On entering a new code into the textbox a popup list appears showing all codes available to the user. Clicking on a code, or pressing <*Return*> will select it, whilst <*Esc*> will hide the list.
Once the codes have been selected press refresh to perform the search.

Once this list has been compiled it can be printed by clicking the print button on the side bar.

5.7.3 Outcome Records

This section describes how to create, edit and delete outcome records. You can create and outcome record from an individual pregnancy only if one or more maternal serum screening reports relating to the pregnancy have already been created, using αlpha.

5.7.3.1 The Outcome Data Entry Screen

As every outcome record is linked to an individual pregnancy the user is required to first search the αlpha database for the patient record using the **Search database** tab in the **Search** section (See Section 5.7.2).

On finding the patient and pregnancy record within the database, the outcome data entry can be opened by double clicking on the patient listing. When another user is editing the outcome record, other users can still open the outcome record in a read only mode.

The data Entry screen is split into **Patient details**, **Outcome details** and **Abnormality codes**. (See Figure 94)

The **Patient details** lists information from the αlpha report for the pregnancy. This should always be checked to make sure the correct patient/pregnancy has been selected. This information cannot be changed.

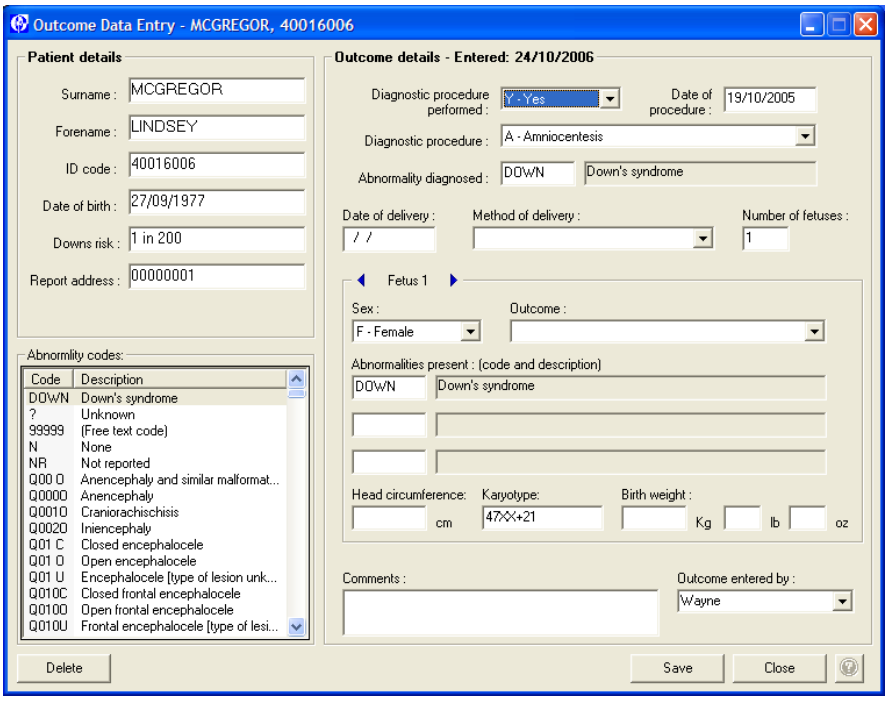


Figure 94: Outcome Data Entry Screen

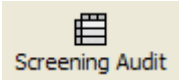
The **Abnormality codes** section lists all ICD and user defined codes for selecting in the abnormality inputs. The user can enter abnormalities by either selecting the code form the list or by typing the code, which will automatically find the code within the list. Pressing <*Enter*> will select the code highlighted in the list. Selecting the code *99999* allows the user to enter a custom abnormality description.

The **Outcome details** section allows the user to enter information regarding:

- Details of any diagnostic procedures, together with abnormalities diagnosed.
- Delivery details,
- Outcome details for 1 or more foetuses:
- Sex
- Foetus outcome
- Up to three abnormalities present
- Head circumference (cm)
- Karyotype
- Birth weight (kilograms or pounds and ounces)
- Comments and the name of the person entering the record.

5.7.4 Screening Audit

The screening audit section is used for monitoring the proportion of screened pregnancies for which outcome information is available, and the uptake of diagnostic procedures such as amniocentesis following screening. It also provides estimates of the detection rates for Down's syndrome and neural tube defects in the screening programme.

To access the Screening Audit section click 

on the icon in the side bar (See Figure 95).

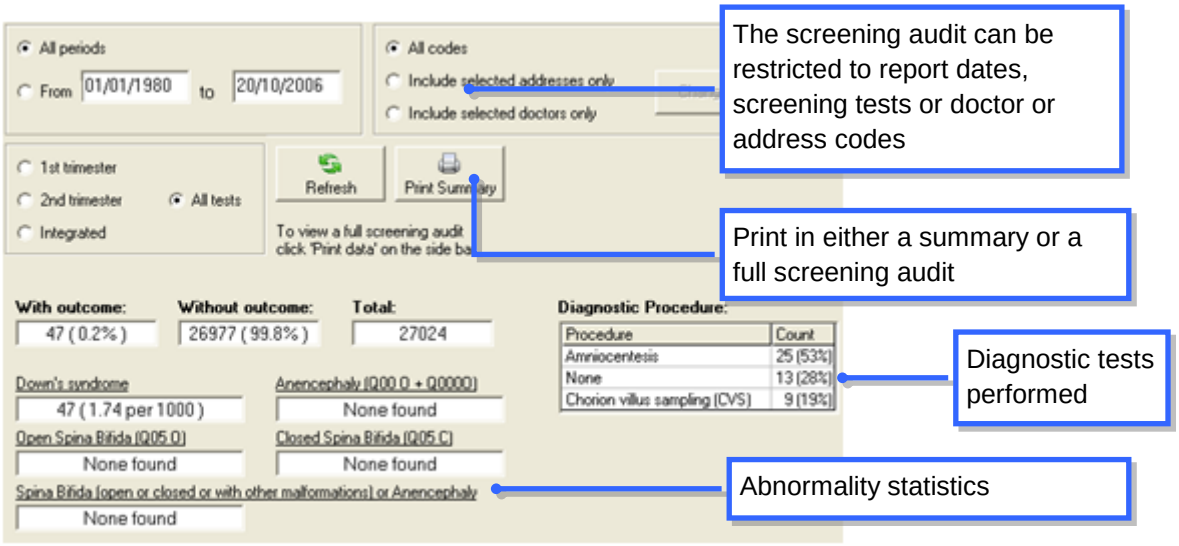


Figure 95: Outcome screening audit

The full screening audit (Figure 96) shows the information in far greater detail categorising the abnormality count according to the screening result (positive, negative, uninterpretable). For positive and uninterpretable screening results, the number of affected pregnancies according to the reason for the positive or uninterpretable result is also shown.

The full report also categorises the diagnostic procedure in the same way. The report also categorises the number of amniocenteses according to risk category shown in a table and plot.

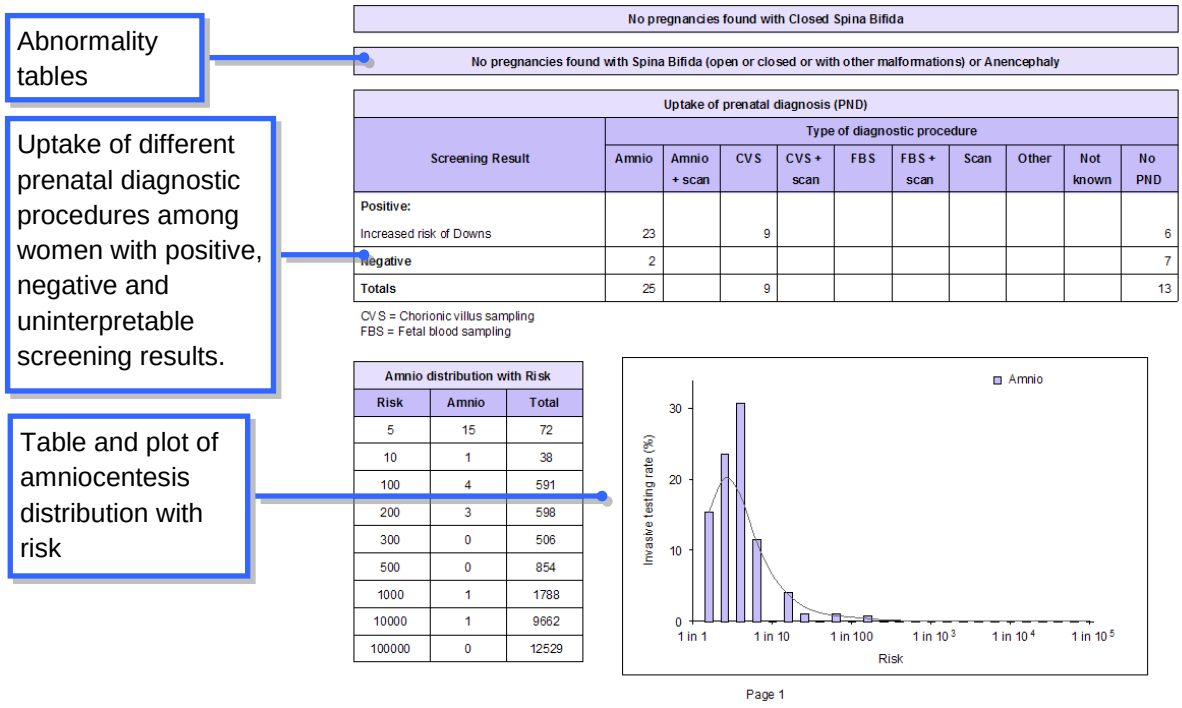
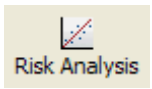


Figure 96: Outcome full screening audit

Studies have shown that the risk of Down's syndrome predicted by αlpha is in close agreement with the observed prevalence of Down's syndrome, in the absence of screening. **αlpha** outcome allows αlpha users to perform this analysis themselves, provided a sufficiently large number of women have been screened.

To access Risk Analysis section click 

on the icon in the side bar.

On selection of a screening test **αlpha** outcome displays a summary showing the number of Down's syndrome pregnancies in each of several predicted risk categories (Figure 97).

Predicted risk category		Median	No. of Down's
> 1 in	4		4
1 in 5 –	140		4
1 in 141 –	190		2
1 in 191 –	550		3
Less than 1 in 550			3
All			16

Figure 97: Outcome risk categories

You can change the predicted risk categories if you wish, by editing the upper limit of each risk category. The number of Downs's cases will be adjusted automatically. Each category should preferably contain 10 or more pregnancies with Down's syndrome, with approximately equal numbers in each category. Risk analysis cannot be performed if the outcome database contains too few cases (less than 10). You can insert and delete categories by clicking on the corresponding buttons on the toolbar. *Refresh* will revert any changes you have made to the risk categories.

When you have specified the predicted risk categories click *Plot* on the toolbar. αlpha outcome will then complete the table and plot the results in a **validation plot**.

The validation plot (Figure 98) includes a line of identity (a straight diagonal line representing perfect risk estimation) overlaid with the median predicted risk plotted against the observed prevalence. This plot can be used to evaluate the performance of screening programmes and the accuracy of risk estimation67.

The screening performance can be assessed by looking at the range of risk covered by the points in the validation plot. A better screening performance is shown by:

- The greater the range of risk estimation, the more discriminatory the test.
- The closer all the points are to the line of identity
- For n risk categories, a greater risk range between the (n-1)th and the nth points.

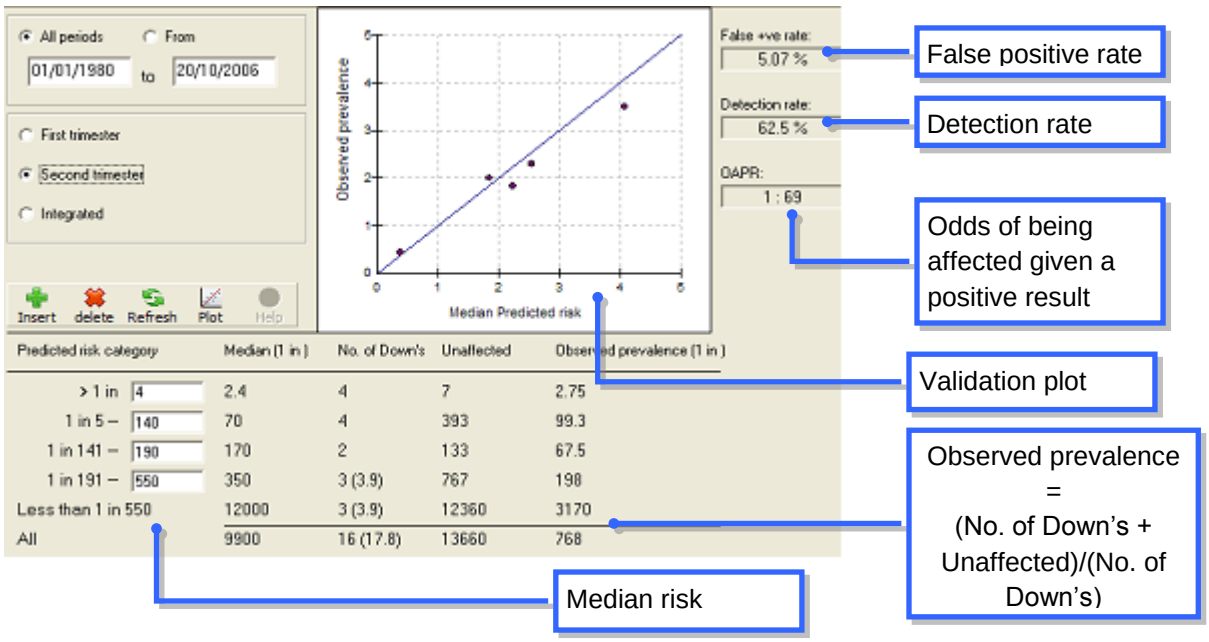


Figure 98: Outcome Validation Plot

5.7.6 Abnormality Codes

αlpha Outcome allows you to record the presence of abnormalities, using the 10th edition of the international classification of diseases (ICD codes).

To view the list of abnormality codes, 

select from the side bar.

This section allows the user to add custom codes, which can be used instead of the ICD code.

To enter a custom code (Figure 99) or make changes to a code click in the *code* column and enter a custom code. You must have a user security level of 5 to make any changes. The code for free text, *99999*, cannot be changed.

Code	ICD Code	Description
DOWN	Q90	Down's syndrome
	?	Unknown
	99999	(Free text code)
	N	None
	NR	Not reported

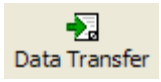
Figure 99: Custom codes

Click Save 

to keep any changes to the list.

5.7.7 Data Transfer

Data transfer is used to export data from the **αlpha** database combined with data from the outcome database.

To access the **Data Transfer** section click 

on the icon on the side bar.

There are three different export file options of an Excel spreadsheet, comma delimited or tab delimited text files.

To transfer data from **αlpha** Outcome, select the file options, the fields you wish to export and then select run to compute the data transfer. For large amounts of data this may take some time.

5.8 Population

The **Population** option shows the maternal age distribution, expected prevalence of various conditions (Down's syndrome, trisomy 18, trisomy 13, SLOS and pre-eclampsia), distribution of ethnic groups and prevalence of smoking, diabetes, previous NTD, IVF, previous Down's and previous pre-eclampsia in the screened population. Selected tests (first trimester, second trimester, integrated, sequential or all tests) and women of selected ethnic groups can be included in the report. You can select the date range for the report and whether screening reports associated with selected report addresses, doctors or sonographers be included or excluded from the analysis (see section 5.13.2 for further information). Figure 100 shows an example of the **Population** screen. The results can be printed with the **Print** button.

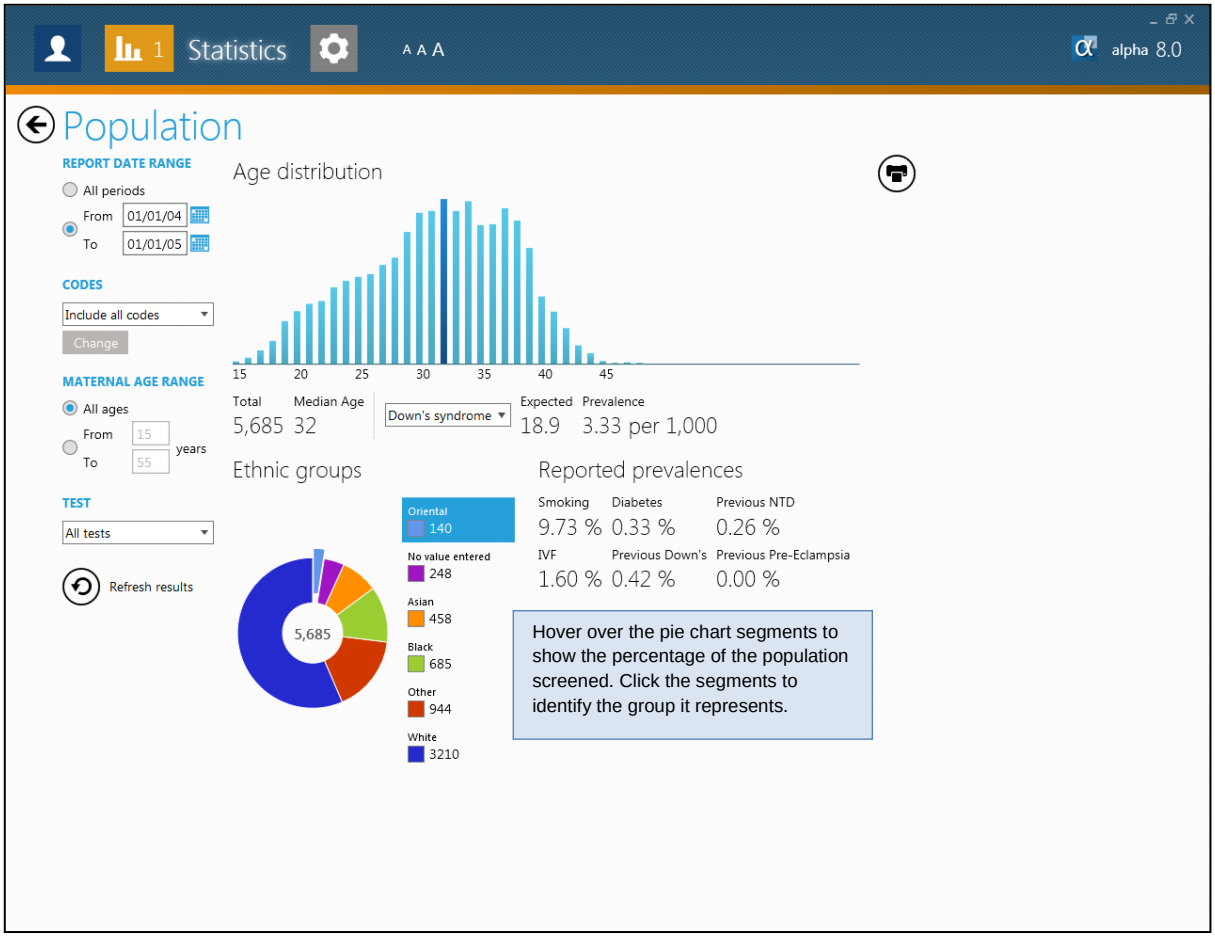


Figure 100: Population

5.9 Regressions

Using the **Regressions** option you can derive new coefficients for calculating the expected median values of the screening markers and AF-AFP, and for adjusting maternal serum MoM values for maternal weight. The options available on the **Regressions** screen will depend on the screening markers installed in **αlpha**.

The information required for regressions can, once a satisfactory number of reports have been produced and stored in the database, be transferred automatically from the corresponding tabulation (See section 5.2). Alternatively, the information required can be entered manually. This process may be followed when the marker is first being used in **αlpha** or when a change to a different formulation of the marker is being carried out.

αlpha can update median or weight correction equations, if you wish, following a regression.

5.9.1 Regressions with gestational age or crown-rump length

The tabulation information is transferred to the regression facility by pressing the **Regression** button in the **Tabulation** screen. Figure 101 shows the regression of the data shown in Figure 116.

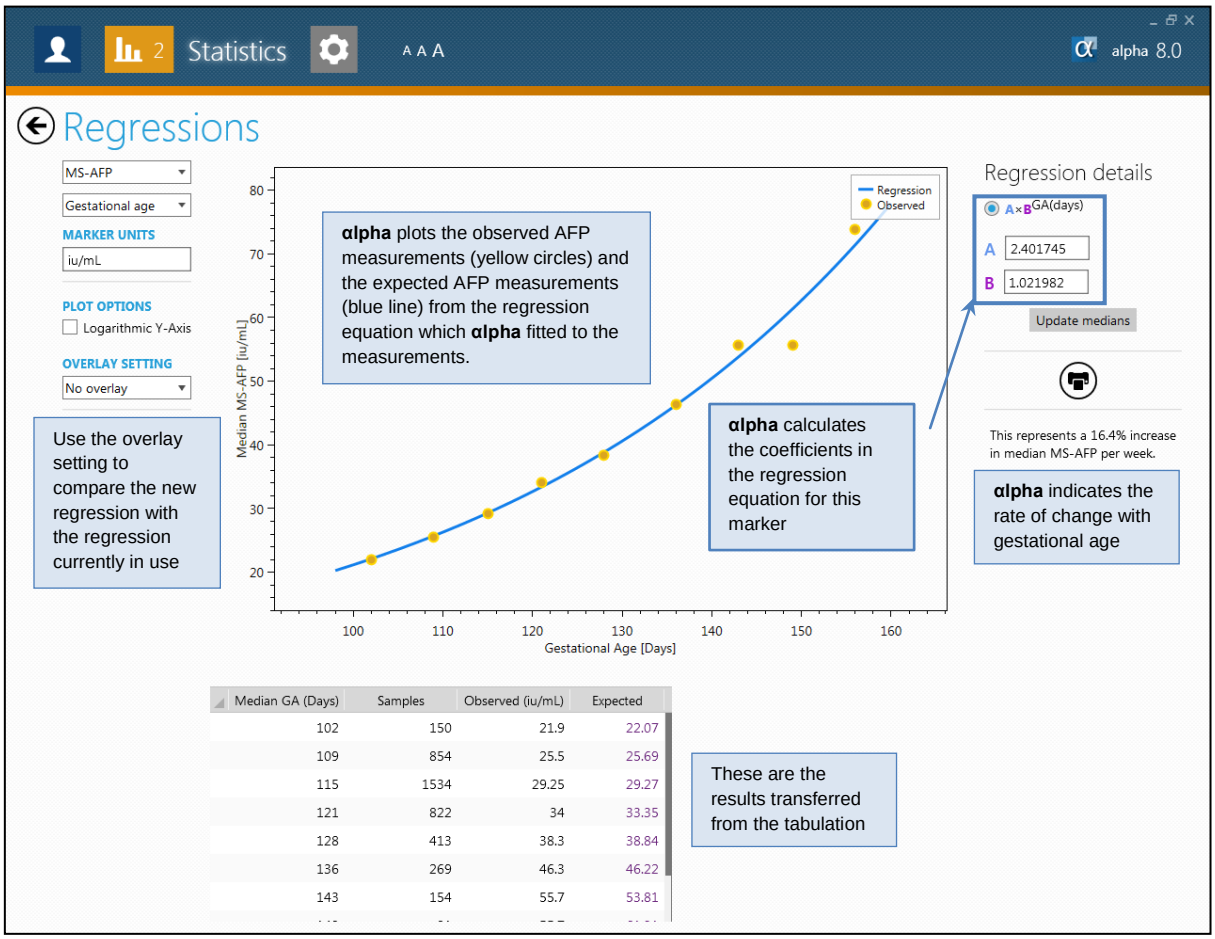


Figure 101: Regression of MS-AFP with gestational age

If the data is to be entered manually, a table should be prepared showing for each gestational age or CRL group the number of samples and median marker level (See section 3.13.3). When the **Regressions** option is selected a blank table is provided into which this information is entered. Once the table contains three or more complete rows of data (gestational age, observed median and number of samples if known) **αlpha** displays the regression curve and coefficients of the regression as shown in Figure 101. The expected (regressed) median values in the table are also updated automatically as you enter or add data.

Use the graph and the table of expected and observed values to examine the goodness of fit of the regression. Large deviations between observed and expected values should be considered in relation to the number of samples on which each value is based.

The slope of the regression line derived from the tabulated measurements is a further indication of suitability for use in screening; NT measurements tend to increase with gestational age, usually at a rate of about 15-25% per week. Standard deviations and slopes that differ markedly from the usual values may be a prompt for further investigation.

When deriving a regression of AF-AFP with gestation, you have the option of excluding AF-AFP levels before 15 weeks, 3 days from the regression. This is because a log-linear regression may overestimate the observed AF-AFP values before 15 weeks8. If you choose to exclude values before 15 weeks, they are not used in deriving the regression equation, but **αlpha** prints the expected AF-AFP levels at 13 weeks, 3 days and at 14 weeks, 3 days in the table of observed and expected values. You can use the expected values to calculate the percentage by which the regressed medians at 13 weeks, 3 days and 14 weeks 3 days should be reduced when calculating AF-AFP MoM values *(See Section* 3.1.9*)*

The graph can be shown with a logarithmic y-axis by selecting the Plot Option Logarithmic Y-axis. With this option selected, data which fits to a log-linear relationship will be displayed as a straight line. The overlay setting can be used to compare overlay the regression currently in use.

Press the **Print** button for a printed copy of the regression.

5.9.2 Regressions with weight

Maternal weight regressions are only needed if **Weight** has been chosen as a data entry prompt. AF-AFP MoM values and MoM values of ultrasound markers such as nuchal translucency are not weight corrected.

The weight tabulation information is transferred to the regression facility by pressing the **Regression** button in the **Tabulation** screen. Figure 102 shows the regression of the data shown in Figure 118.

If the data is to be entered manually, a table should be prepared showing for each weight group the observed median MoM values, unadjusted for weight. (See section 3.13.3.3). When the **Regressions** option is selected a blank table is provided into which this information is entered. Once the table contains three or more complete rows of data (weight, observed median and number of samples if known) **αlpha** displays the regression curve and coefficients of the regression as shown in Figure 102. The expected (regressed) median values in the table are also updated automatically as you enter or add data.

The coefficients displayed are those relating to maternal weight in kilograms, and these are the ones required by **αlpha**. If you have chosen to enter weight in pounds **αlpha** will automatically convert to kilograms for the purposes of the regression, even though weights are printed in pounds on the reports.

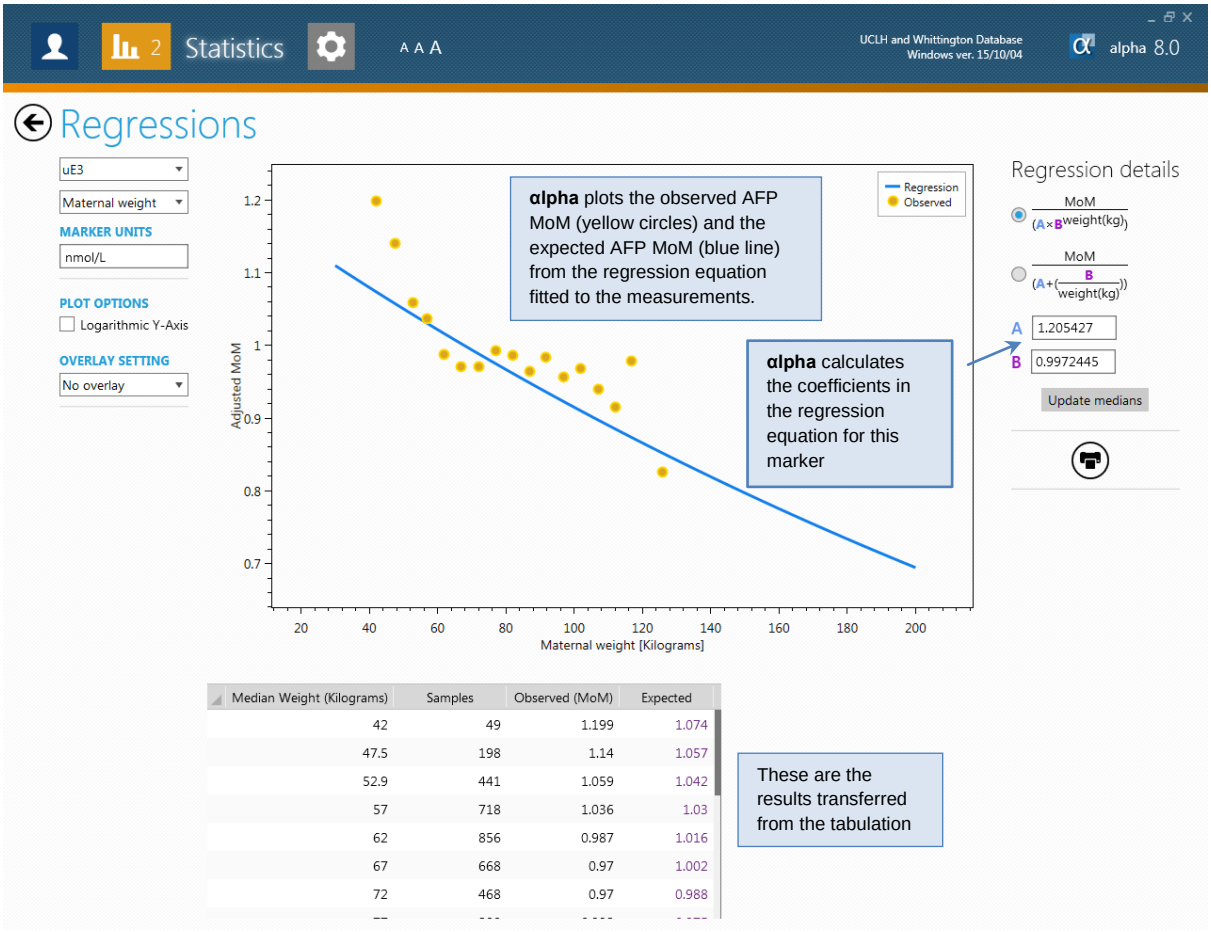


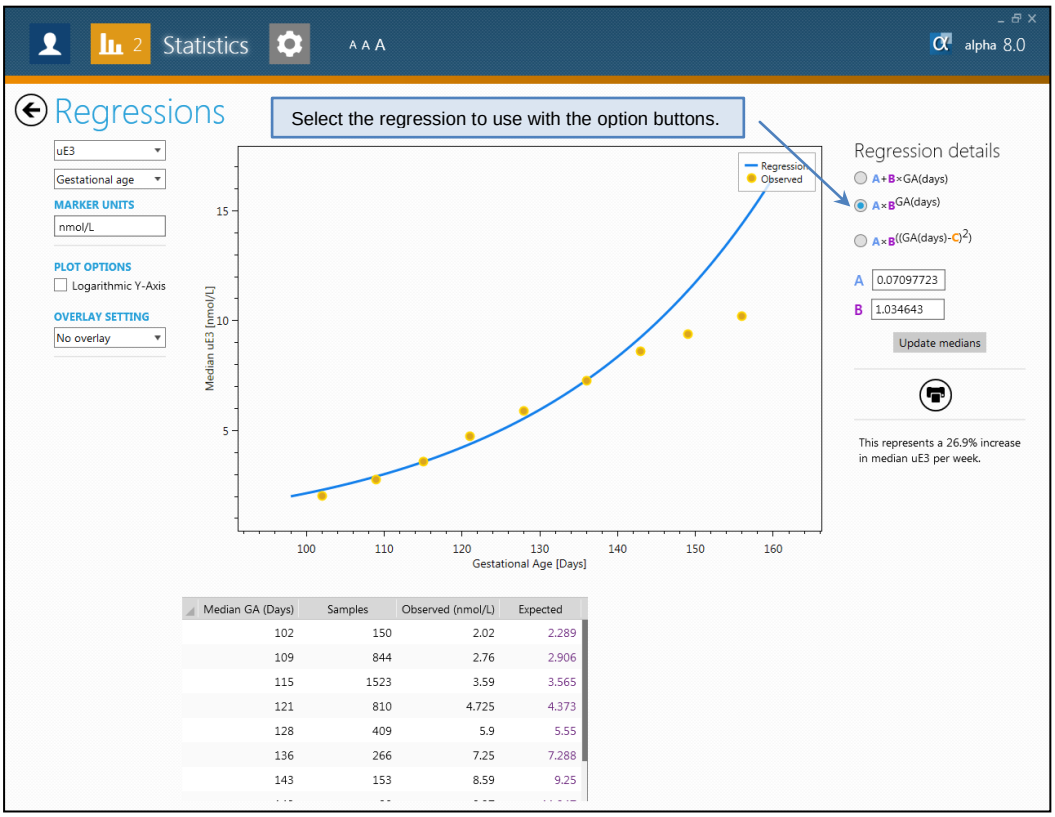
Figure 102: Regression of uE3 MoM with maternal weight (log-linear equation)

5.9.3 Changing the equation used in the regression

For some markers more than one regression equation relating measurement to gestation age is available. (See *Appendix* D *Equations used in calculations)*. Users can choose which equation fits their data best.

Figure 103 shows a comparison of the log-linear and log-quadratic regression equations for uE_3. Use the graph and the table of expected and observed values to examine the goodness of fit of the regression. Large deviations between observed and expected values should be considered in relation to the number of women on which each value is based.

For regressions with maternal weight you can specify either a log linear regression [13], or alternatively a linear reciprocal regression [26]. Although there is little to choose between the two models, some users may find that one model fits their data better than the other. The log-linear model is the one most widely used.



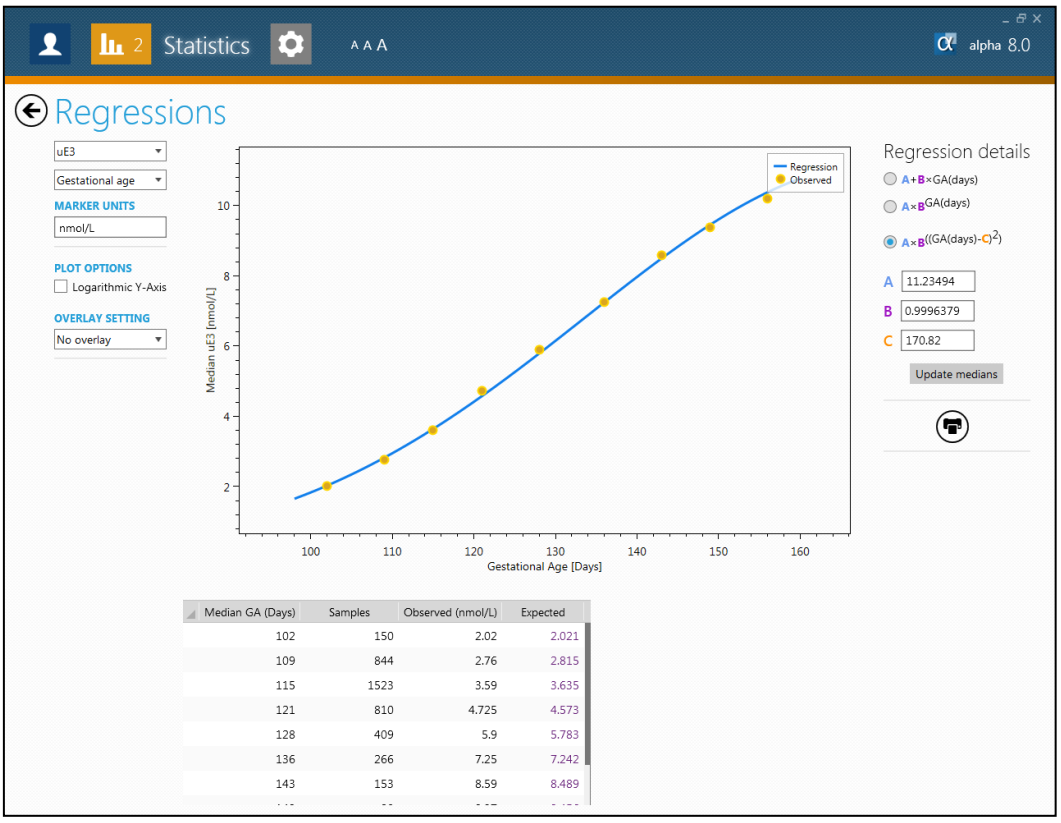


Figure 103: Comparison of log quadratic and log cubic equations for uE_3

5.9.4 Updating median equation coefficients

If you judge that the regression represents a satisfactory estimate of the median values or weight corrections in your population, press the **Update Medians** button. A window similar to the one shown in Figure 104 will be shown. If ethnic group specific medians have been derived select the checkbox alongside the name of the group to update the coefficients for that group only.

Press the **Update** button to update the selected coefficients. The new coefficients will be used from date and time on which they are updated. The current and historical coefficients can be viewed using **Coefficients** in the **Setup** screen (See section 3.2).

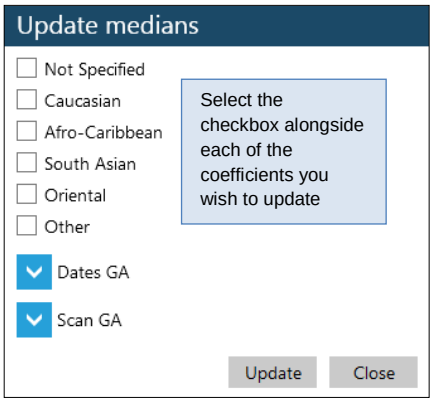


Figure 104: Update medians

Sonographer-specific medians can be updated from a regression made from a tabulation according to crown-rump length (CRL) for nuchal translucency. When the **Update Medians** button is pressed a window similar to that in Figure 105 is shown. Open the Sonographer Specific section and select the checkbox alongside the sonographer whose medians you wish to update. Press the **Update** button to update the selected coefficients. The new coefficients will be used from date and time on which they are updated.

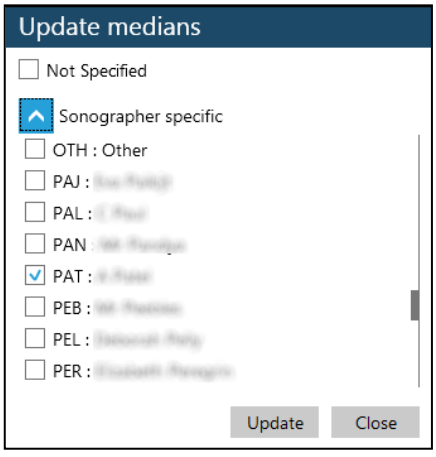


Figure 105: Update sonographer specific medians

5.10 Report summary

The **Report summary** option helps you to monitor the number of screening and diagnostic tests processed in a specified time period. It provides a breakdown of the number of reports according to the screening or diagnostic result. Selected tests (first trimester, second trimester, integrated, sequential or all tests) and women of selected ethnic groups can be included in the report. You can select the date range for the report and screening reports associated with selected report addresses, doctors or sonographers be included or excluded from the analysis.

You can monitor the effect of repeat testing and scan updates (tests that are reinterpreted on the basis of ultrasound scan information added after the initial screening result) by examining tables which show how the results changed following the second report.

When the **Report Summary** option is first selected the screen in Figure 106 is shown. Once the options have been selected and the **Refresh** button pressed a screen similar to that in Figure 107 is shown.

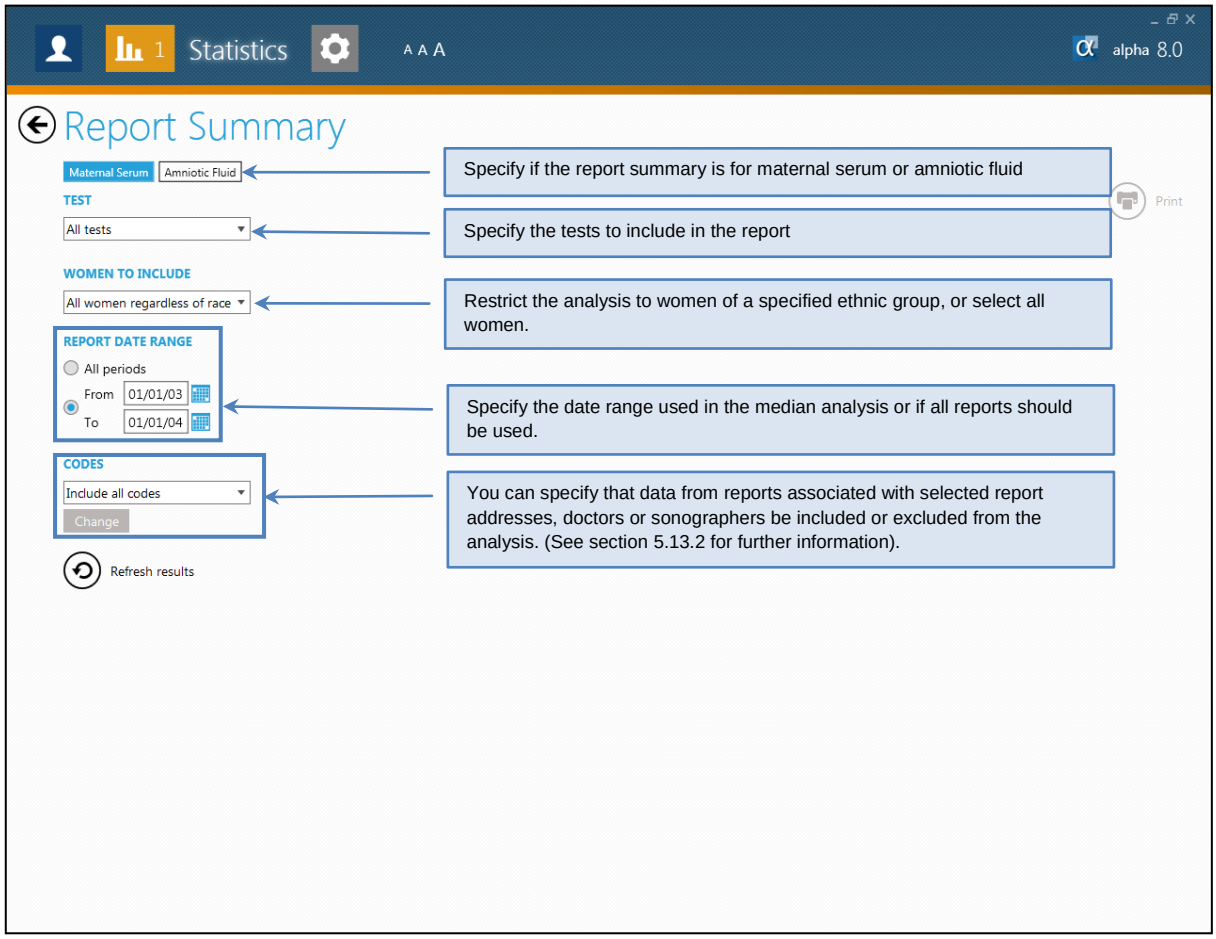


Figure 106: Options in Report Summary

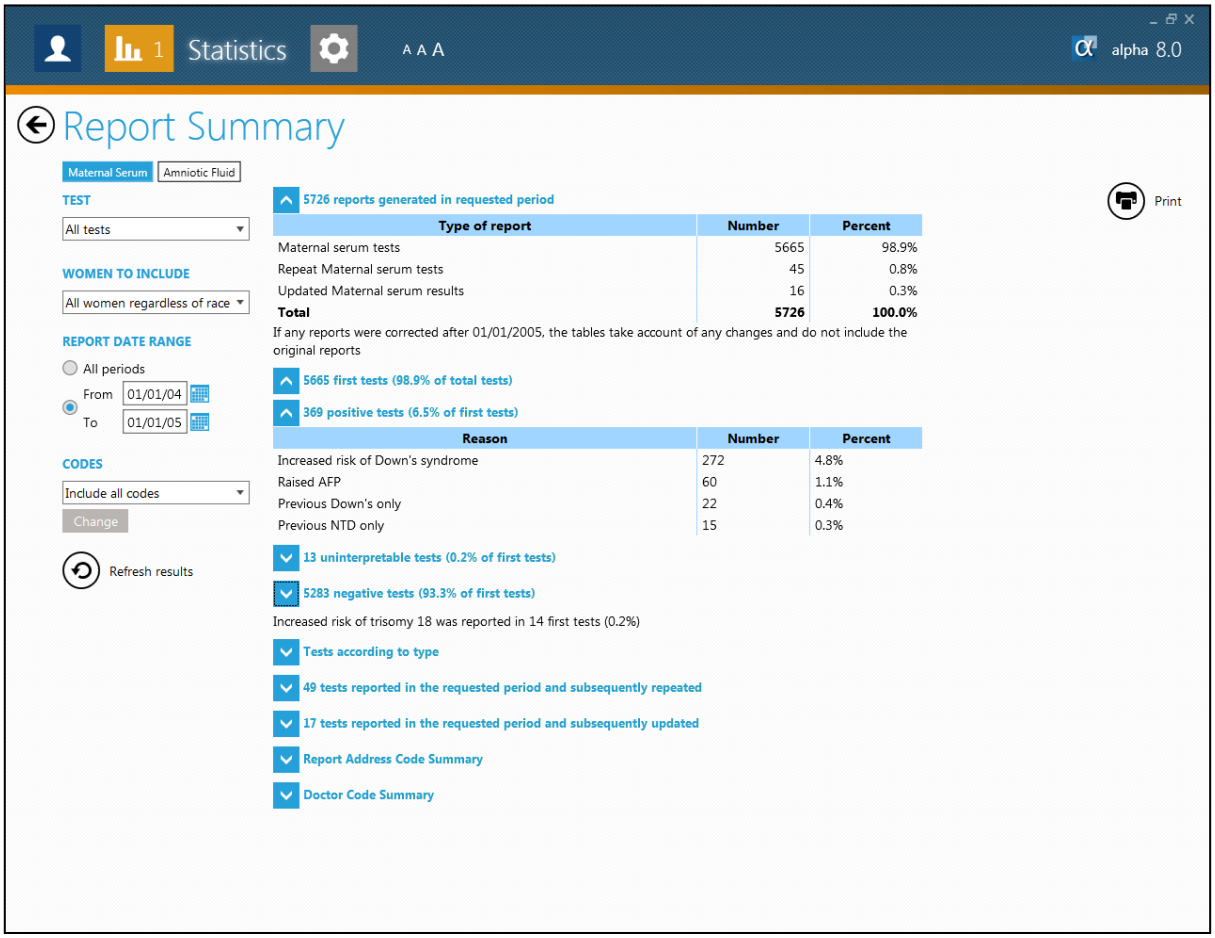
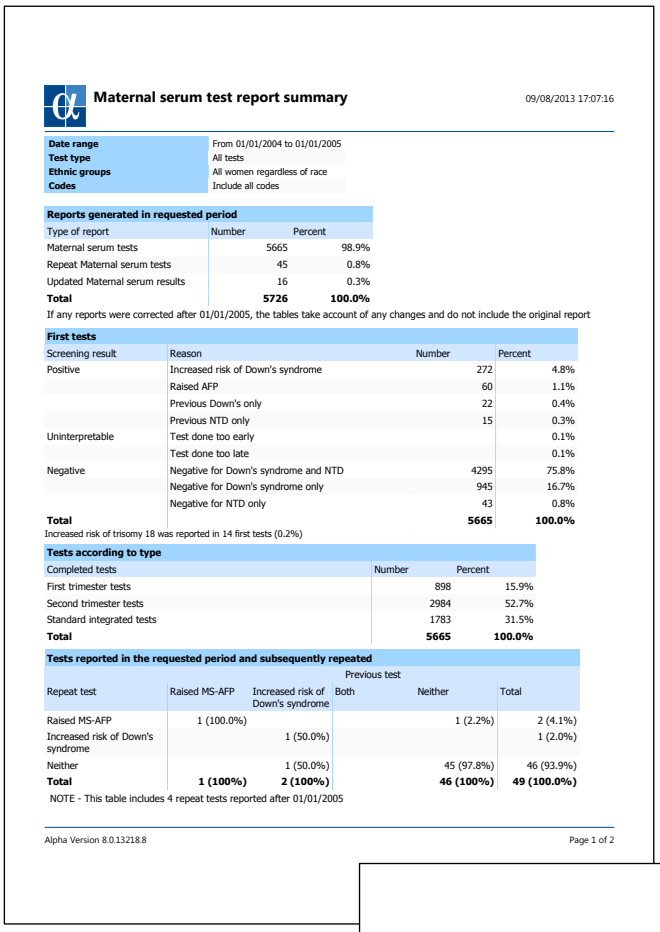


Figure 107: Report Summary

The **Report Summary** screen gives an overview of the screening report. The detail of each section can be seen by opening the expander by pressing on the next to the title and can be hidden by pressing .

When the **Print** button is pressed a report similar to that in Figure 108 is shown. The figure shows the meaning of the tables presented.



Maternal serum test report summary

09/08/2013 17:07:16

Date range	From 01/01/2004 to 01/01/2005
Test type	All tests
Ethnic groups	All women regardless of race
Codes	Include all codes

Reports generated in requested period

Type of report	Number	Percent
Maternal serum tests	5665	98.9%
Repeat Maternal serum tests	45	0.8%
Updated Maternal serum results	16	0.3%
Total	**5726**	**100.0%**

If any reports were corrected after 01/01/2005, the tables take account of any changes and do not include the original report

First tests

Screening result	Reason	Number	Percent
Positive	Increased risk of Down's syndrome	272	4.8%
	Raised AFP	60	1.1%
	Previous Down's only	22	0.4%
	Previous NTD only	15	0.3%
Uninterpretable	Test done too early		0.1%
	Test done too late		0.1%
Negative	Negative for Down's syndrome and NTD	4295	75.8%
	Negative for Down's syndrome only	945	16.7%
	Negative for NTD only	43	0.8%
Total		**5665**	**100.0%**

Increased risk of trisomy 18 was reported in 14 first tests (0.2%)

Tests according to type

Completed tests	Number	Percent
First trimester tests	898	15.9%
Second trimester tests	2984	52.7%
Standard integrated tests	1783	31.5%
Total	**5665**	**100.0%**

Tests reported in the requested period and subsequently repeated

			Previous test		
Repeat test	Raised MS-AFP	Increased risk of Down's syndrome	Both	Neither	Total
Raised MS-AFP	1 (100.0%)		1 (2.2%)		2 (4.1%)
Increased risk of Down's syndrome		1 (50.0%)			1 (2.0%)
Neither		1 (50.0%)	45 (97.8%)		46 (93.9%)
Total	**1 (100%)**	**2 (100%)**	**46 (100%)**		**49 (100.0%)**

NOTE - This table includes 4 repeat tests reported after 01/01/2005

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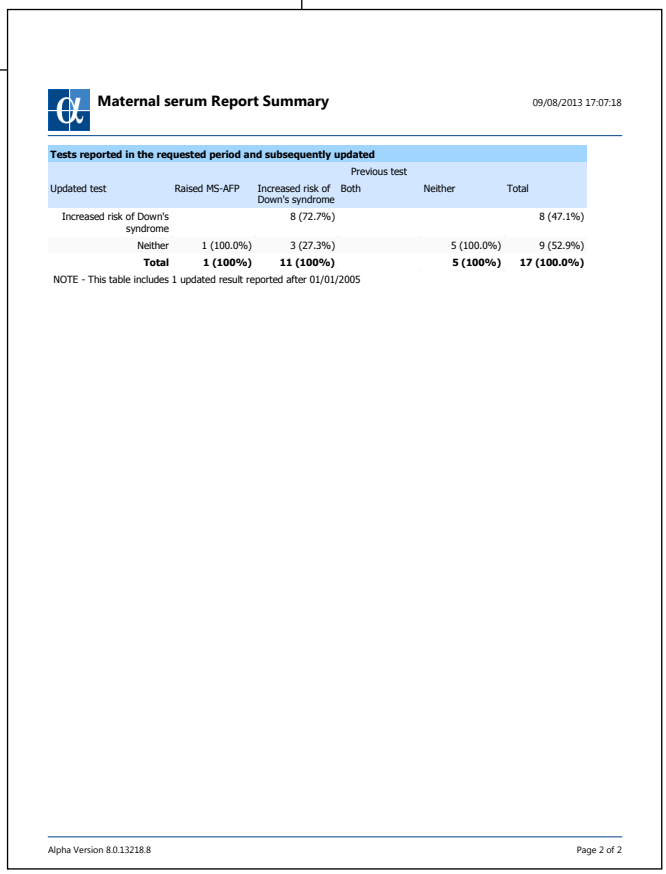

Maternal serum Report Summary

09/08/2013 17:07:18

Tests reported in the requested period and subsequently updated

			Previous test		
Updated test	Raised MS-AFP	Increased risk of Down's syndrome	Both	Neither	Total
Increased risk of Down's syndrome		8 (72.7%)			8 (47.1%)
Neither	1 (100.0%)	3 (27.3%)		5 (100.0%)	9 (52.9%)
Total	**1 (100%)**	**11 (100%)**		**5 (100%)**	**17 (100.0%)**

NOTE - This table includes 1 updated result reported after 01/01/2005

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The number of first tests, repeat tests and scan updates in the selected period

This table provides a breakdown of first tests according to the reported screening or diagnostic result. This table can be used to determine the screen positive rate. The table also indicates the number of tests in which a high risk of trisomy 18, trisomy 13 or Smith-Lemli-Opitz syndrome was reported.

This table shows the type of tests carried out

Further tables show how the screening or diagnostic result changed following a repeat sample or a scan update.

Figure 108: Report Summary

5.11 Risk Analysis

The **Risk Analysis** option presents in a graphical format a cumulative total of the number and percentage of screening reports with risks greater than or equal to various cut-off levels. When this option is selected a screen similar to that in Figure 109 is shown. You can select for which conditions (Down's syndrome, NTD, trisomy 18, trisomy 13, SLOS and pre-eclampsia) and which tests (first trimester, second trimester, integrated, sequential or all tests) should be included in the analysis. You can also select the date range for the report and screening reports associated with selected report addresses, doctors or sonographers be included or excluded from the analysis (See Section 5.13.2).

The results in Figure 109 show that 5645 tests were carried out in the period selected and that 292 (5.17%) had a risk greater than the cut-off (1 in 250). The cut-off can be changed by moving the orange line on the graph and the results are automatically updated.

The results can be printed by pressing the **Print** button. They are presented as a table which cut-offs from 1 in 10 to 1 in 500 in risk bands of 1 in 10. You can use this table to examine the screen positive rate corresponding to different risk cut-off levels, and to determine the risk cut-off required to yield a given screen positive rate.

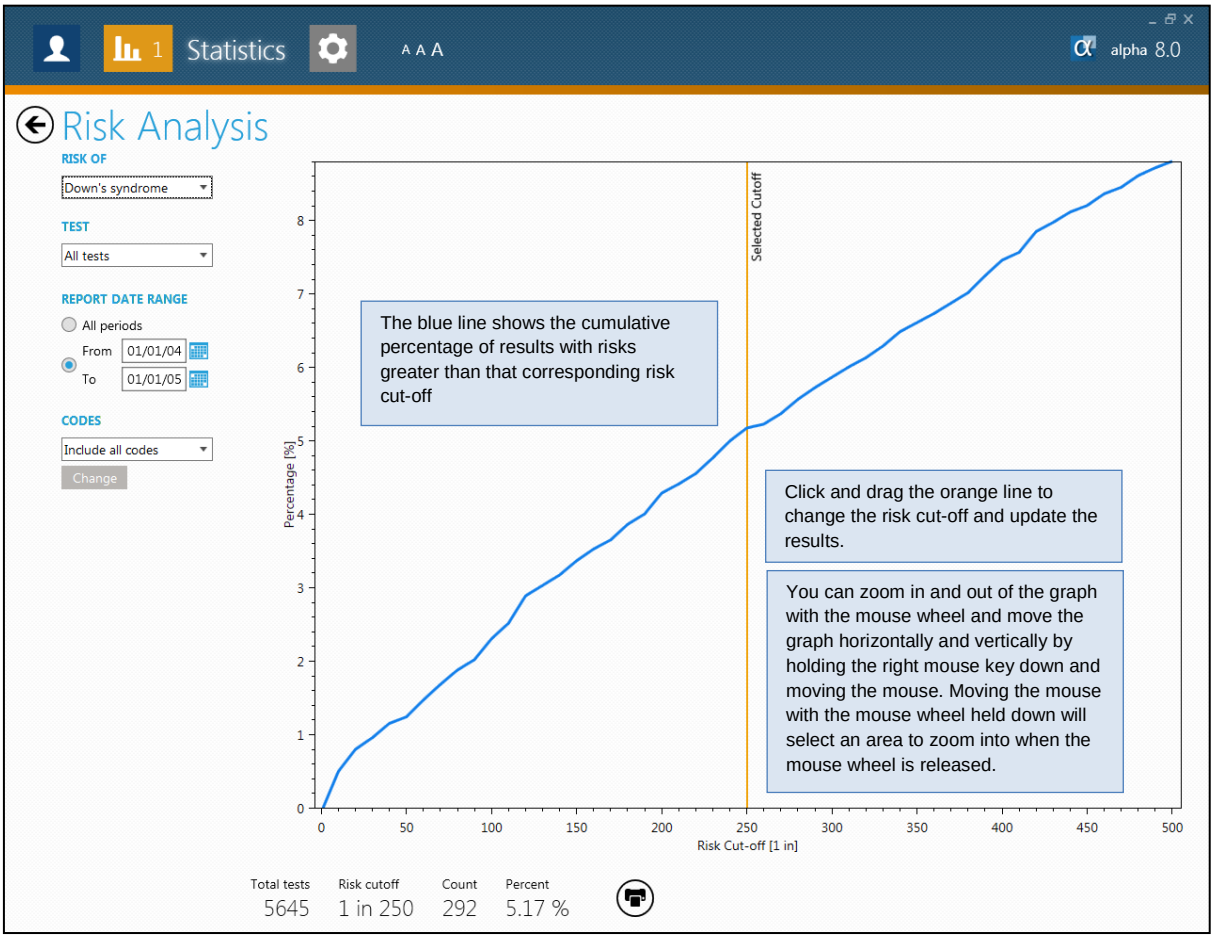

Figure 109: Risk Analysis

5.12 Screening performance

With the **Screening Performance** option **αlpha** can calculate estimates of the expected screening performance given the age distribution of the screened population. With this option you can monitor differences between the observed and expected median values. When this option is selected the screen in Figure 110 is shown.

The screening performance for Down's syndrome, trisomy 18, trisomy 13, SLOS and pre-eclampsia can be calculated. The age distribution used can either be that of the screened population or from maternities in England and Wales for selected years. If the age distribution of the screened population is used then there are additional options provided for selecting the age range, the range of report dates to use to provide the age distribution and whether reports associated with selected report addresses, doctors or sonographers be included or excluded from the analysis. The age distribution is not used when calculating the screening performance for pre-eclampsia.

The results can be displayed as:

- The detection rate and false positive rate achieved at fixed cut-off values
- The detection rate and corresponding cut-off value at fixed fixed positive rates
- The false positive rate and corresponding cut-off value at fixed detection rates

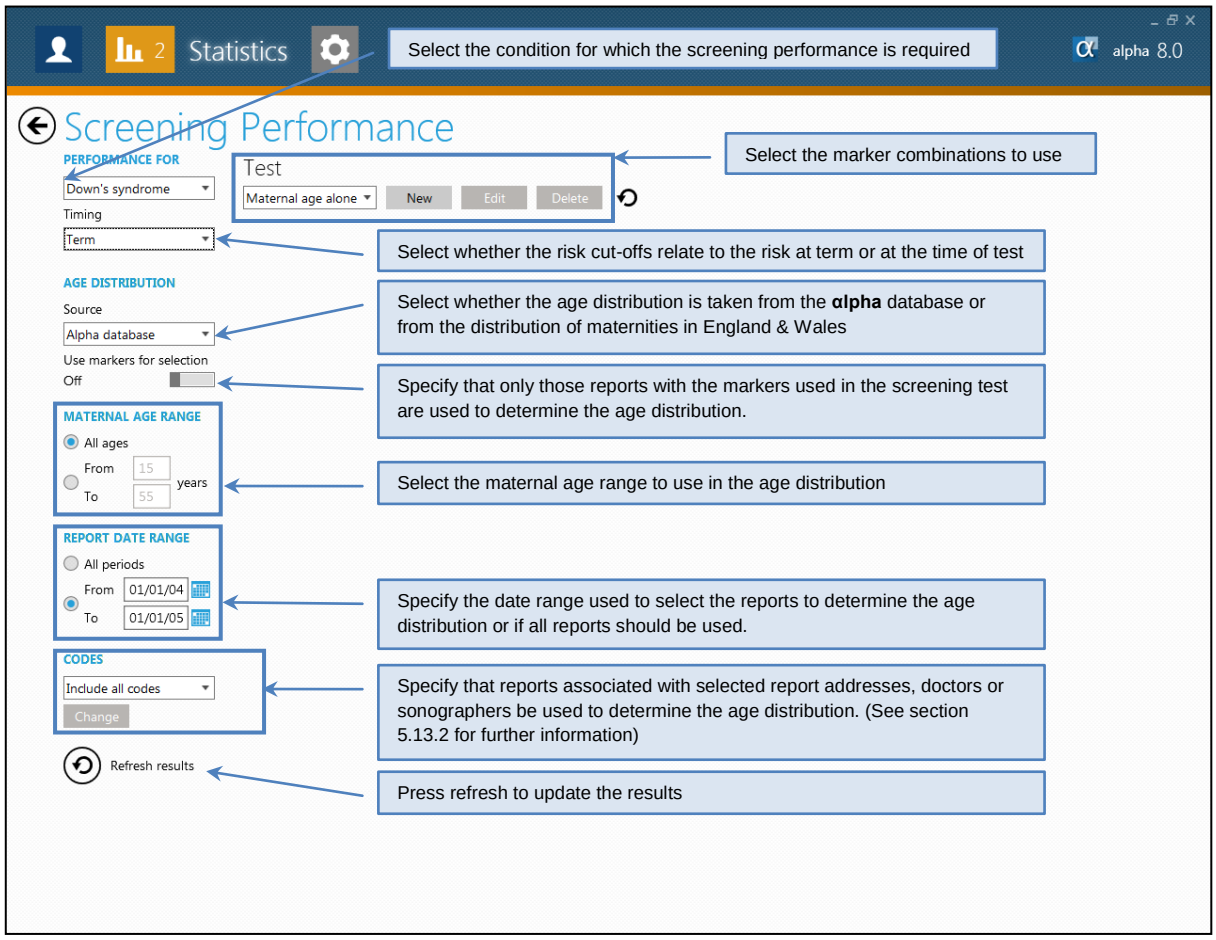

Figure 110: Screening Performance

The first time you use the **Screening Performance** option the only screening test for which performance estimates are available is **Maternal Age Alone.** To obtain estimates of screening performances for other tests (for example the quadruple test) you need to select the markers to use for each test. To do this press the **New** button and the window in Figure 111 containing a list of the available screening markers will be shown. Select the markers required and if necessary whether the test is an Integrated or Sequential test. Repeat this procedure for each test for which you require estimates of screening performance. The **Edit** button allows the marker combination to be edited and **Delete** will delete it.

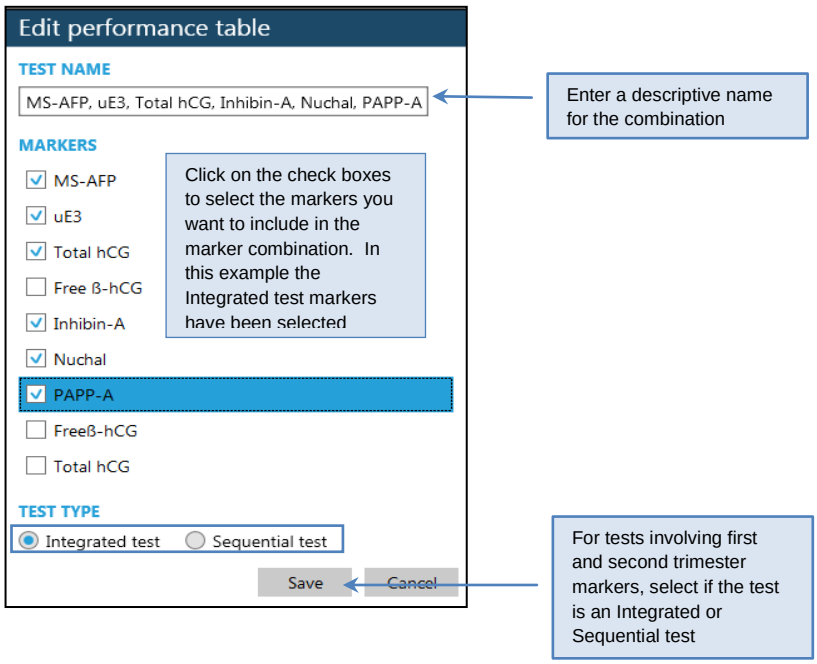

Figure 111: Specify markers to use for screening performance table

Select the name of the marker combination from the **Test** dropdown and press **Refresh** or to show the selected screening performance table (See Figure 112) for the age distribution of England and Wales in 2006 to 2008. The screening performance table is shown in four columns:

Cut-off : The risk cut-off (**Timing** specifies if this is at term or time of test)
DR: Detection rate with this cut-off
FPR: False positive rate with this cut-off
OAPR: Odds of being affected given a positive result at this cut-off.

The screening performance can also be calculated using statistical parameters based on dates or scan gestation and with or without adjustment for maternal weight.

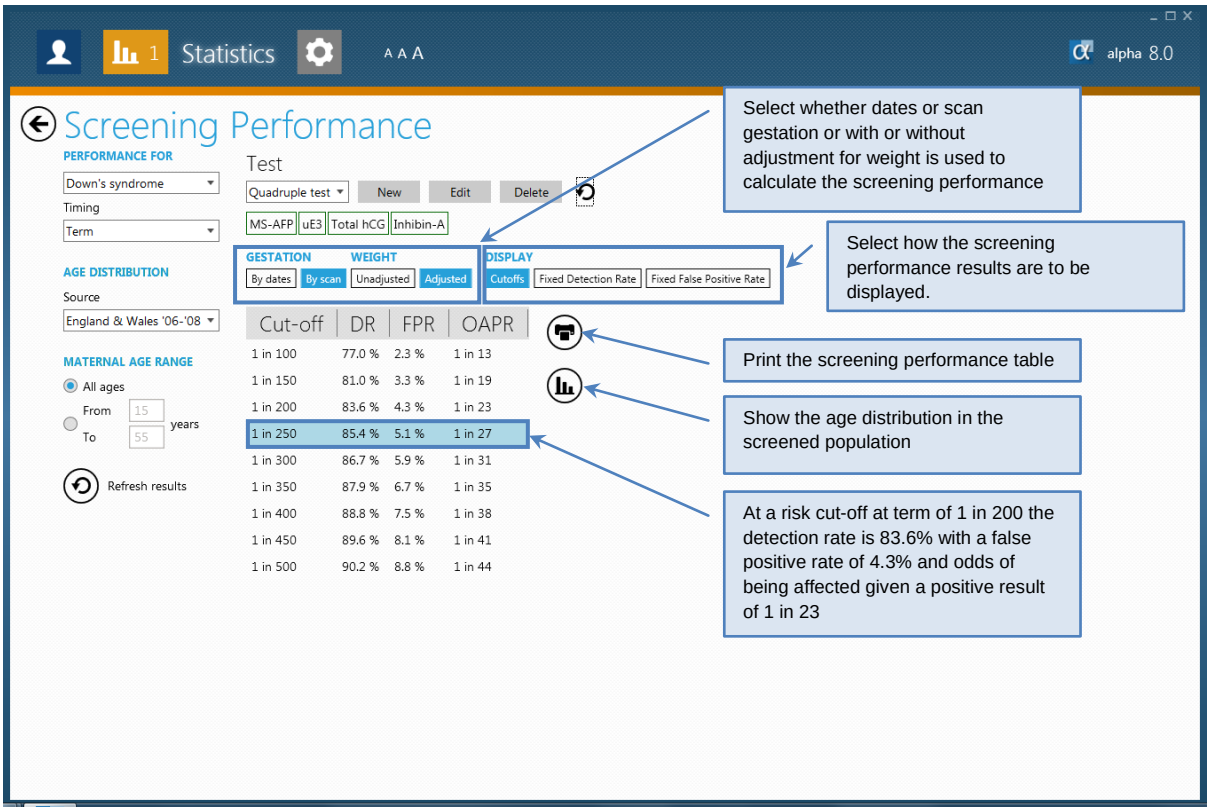

Figure 112: Screening performance table for quadruple test

Figure 113 shows a screening performance table for the Integrated test using the age distribution from the screened population. The screening performance at 10, 11, 12 and 13 weeks of gestation or (as in this case) the average gestation for the screened population can be displayed. The number of tests carried out at each week of gestation is also shown.

Press the **Print** button for a printed copy of the **Screening Performance.** The age distribution used for the screening performance table can be seen by pressing the **Population** button (See section 5.7).

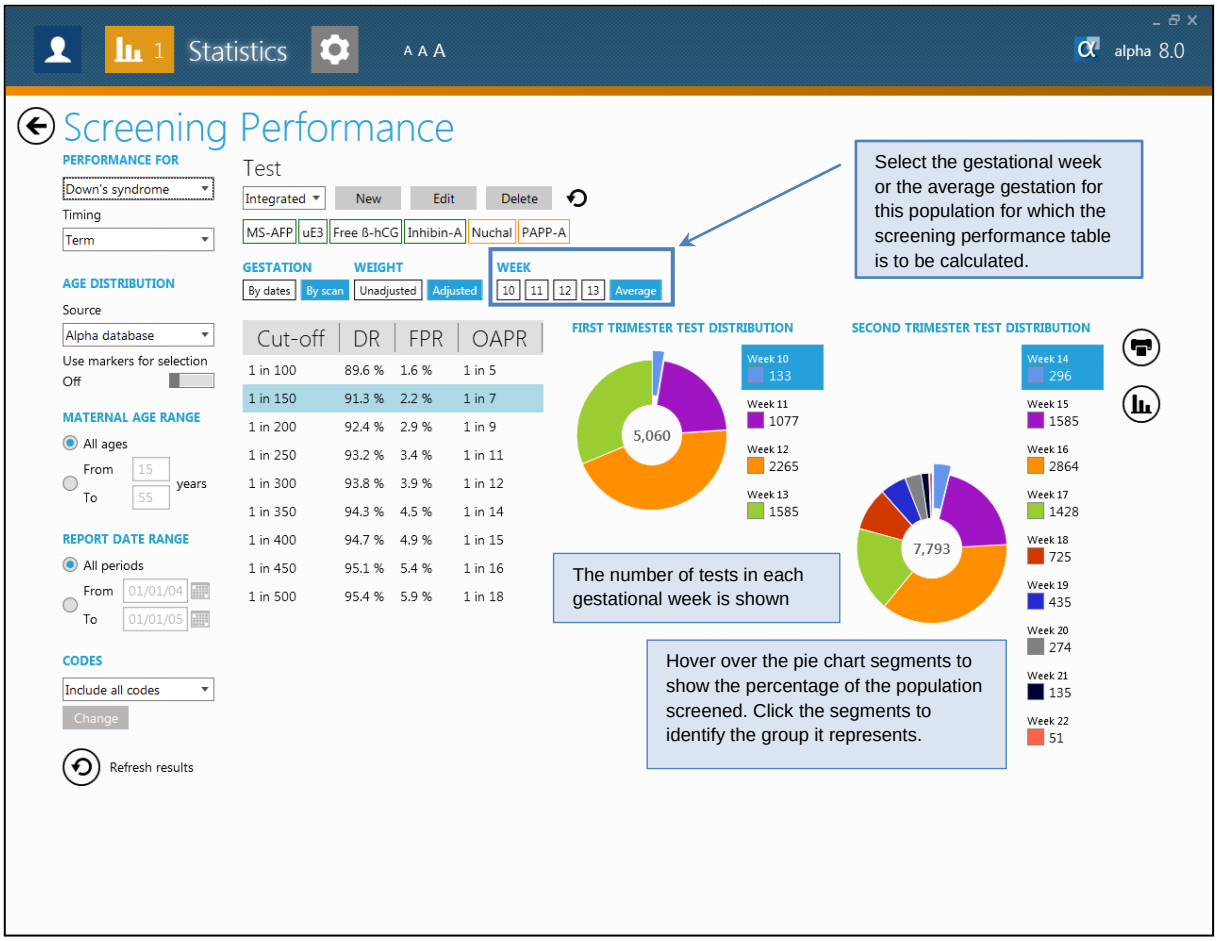

Figure 113: Screening performance table for Integrated test

5.13 Tabulations

Using the **Tabulations** option you can monitor the variation of the serum marker and AF-AFP with gestational age or NT with CRL and check the accuracy with which the normal median equations are estimating the expected marker levels. Tabulated data on screening markers and AF-AFP can also be passed automatically to the **Regression** section (see Section 5.9) in order to recalculate new values for regression equation coefficients (see Section 5.9).

The tabulation of nuchal translucency with crown-rump length can be used as an indication of whether an individual sonographer's NT measurements are acceptable for use in screening. The tabulation displays both the rate of increase of NT with gestational age, and the estimated standard deviation of the NT MoM values (expressed in $\log_{10}$). These can then be compared with published estimates (for example, those in reference [88]).

The options available on the **Tabulations** screen will depend on the screening markers installed in **αlpha** (See Figure 114).

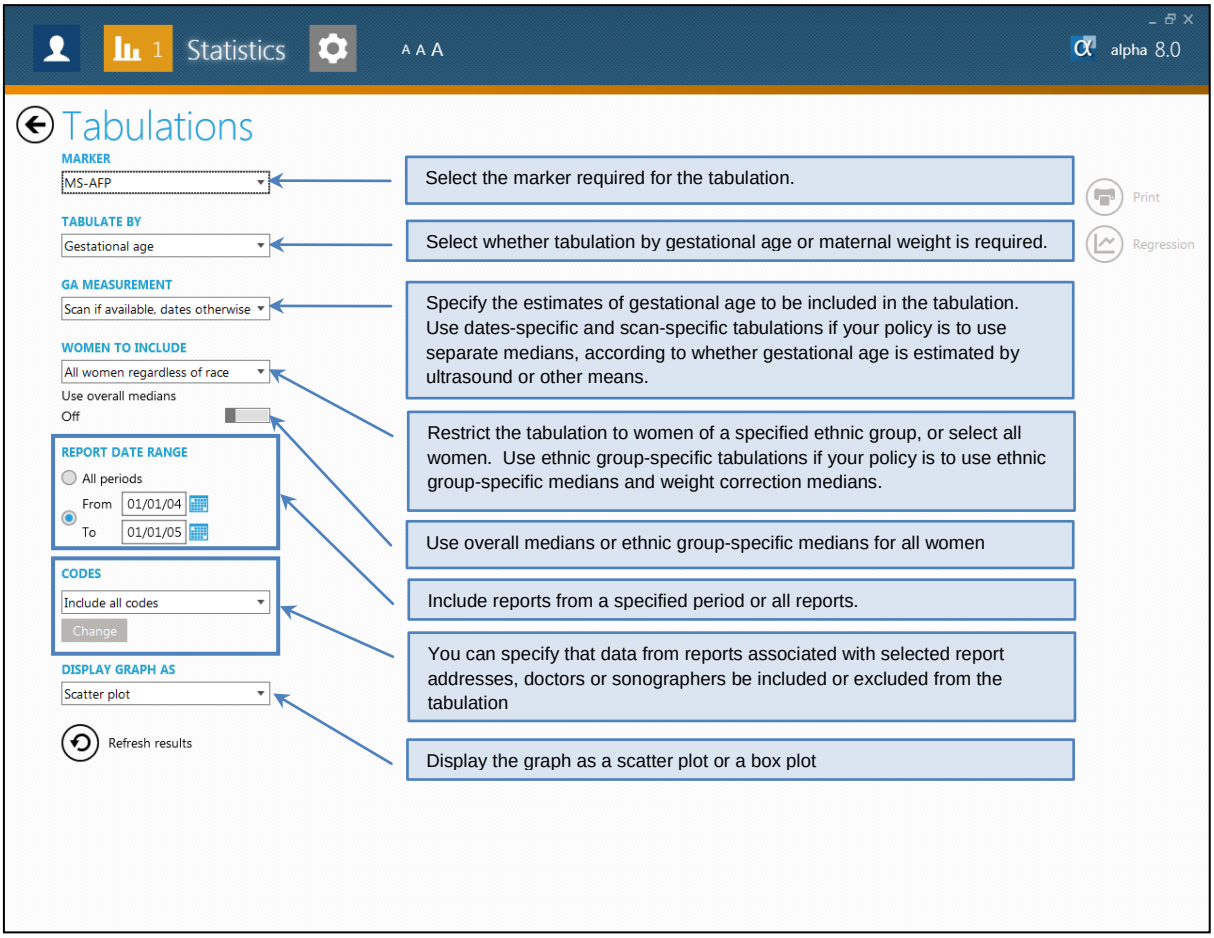

Figure 114: Tabulation options

5.13.1 Setting-up tabulations

For each type of tabulation, you can specify a number of options to select the data you want (for example, data relating to Caucasian women screened during 2013).

In order to specify the date range over which to tabulate the data you can either select all periods (which will include all eligible data in the database) or you can specify start and end dates. Records are included in the tabulation if the date of reporting falls within the requested period.

If you have included the **Ethnic group** prompt in your screen design, you can choose to produce separate tabulations (of maternal serum markers only) for each ethnic group, or for all women, regardless of ethnic group. *See section 5.13.6 for an explanation of how **alpha** tabulates the data in this case.*

Depending on the circumstances, some reports may be excluded from tabulations automatically. Reports for women who smoke, for women with diabetes or a multiple pregnancy are excluded. Repeat tests, re-interpreted reports and reports that have been deleted are also excluded. Reports that have been corrected are also excluded, however, the correct version of the report will be included if it is otherwise eligible. Reports that are uninterpretable for the purposes of the current tabulation are also excluded.

For tabulations with gestational age, any reports that are based only on a clinical estimate of gestational age are excluded. When tabulating with gestational age estimated by 'dates' (LMP), dates classed as uncertain are also excluded. Dates are regarded as uncertain when they are recorded as such, or when oral contraceptive use is recorded less than 60 days before the first day of the LMP, or when only the month, and not the exact day, of the LMP or EDD is recorded.

5.13.2 Restricting reports to specified doctors, addresses of sonographers

If you want to restrict the tabulation to specified doctors, addresses or sonographers, select the appropriate option in the **Codes** section of the **Tabulation** screen, and select the "**Change**" button to specify the doctor, address or sonographer codes you want to include or exclude. A screen similar to the one in Figure 115 is shown for doctors and similar screens are shown for addresses and sonographers.

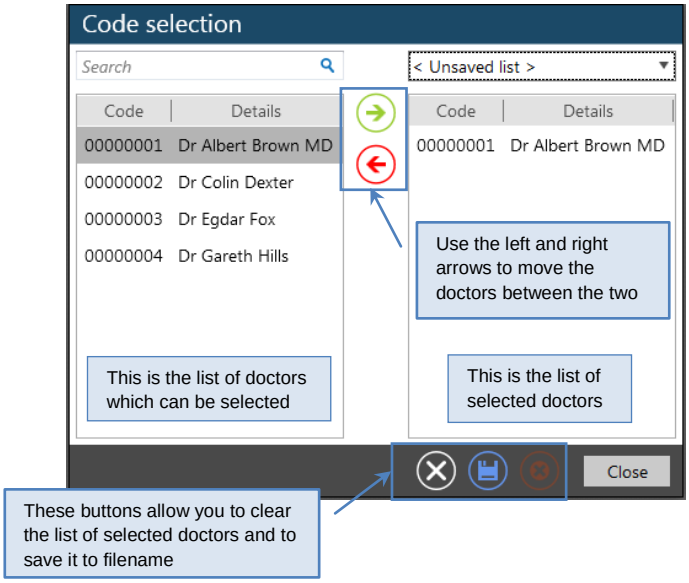

Figure 115: Code selection

5.13.3 Tabulation by gestational age

The **Tabulations** screen provides tabulations according to gestational age for maternal serum markers and AF-AFP.

Except for AF-AFP, you specify, in the **Tabulations** screen, the gestational age estimate **αlpha** should use for tabulating the data. If you use, or intend to use, a single median equation for all women, regardless of the method of estimating gestational age, choose **Scan if available, dates otherwise**. If you use separate median equations for gestational age estimated by dates and by scan, you will need two tabulations, one using **Dates only** and the other **Scan only**.

Select the options you require and press the **Refresh** button to begin the tabulation. **αlpha** displays a preview of the tabulation, as shown in Figure 116.

Figure 116: Tabulation of MS-AFP by gestational age

There are five columns in the tabulation and these are labelled **A** to **E** in Figure 116 and described in Table 12

Table 12: Columns in Tabulation

Column	Content
A	The gestational age at which measurements contained in this group were taken
B	The median gestation in days for each group
C	The number of values tabulated in each group.
D	The median maternal serum marker in concentration units for each group
E	The median maternal serum marker in MoM values for each group. MoM values are recalculated using the specified estimate of gestational age, where necessary. **αlpha** ensures that chronologically correct median equations are selected when recalculating MoM values.

If the overall MoM value lies outside the 95% confidence interval around 1.0 MoM then this will be indicated by the symbol , as in the example in Figure 116. MoM values that are consistently higher or lower than the expected value (1.0 MoM) may indicate that the current estimates of the gestation-specific medians are not accurate, and need revising.

The estimates of the 10th and 90th centiles and the observed standard deviation of the MoM values (transformed to logarithms to the base 10) are also shown (**F** in Figure 116). A standard deviation that differs markedly from published estimates *(see Appendix* J *Statistical parameters: Down's syndrome)* may indicate an assay problem, and prompt further investigation.

Press the **Print** button for a printed copy of the tabulation or the **Regression** button for a regression of the tabulated data. The regression provides the coefficients needed to update the median equations, should you wish to do this *(see Section 5.9 for more information on regressions)*.

5.13.4 Tabulation by crown rump length

Tabulation according to crown-rump length (CRL) is available for the ultrasound marker nuchal translucency (NT).

The principle is the same as for tabulation by gestational age *(see section 5.13.3)* except that the data are tabulated by 5 mm CRL bands and not by completed gestational weeks. Also, there is no option for ethnic group-specific tabulations, and you do not need to specify which estimate of gestational age to use. Figure 117 shows an example of a tabulation of nuchal translucency according to crown-rump length.

There are five columns in the tabulation and these are labelled **A** to **E** in Figure 117 and described in Table 13.

Table 13: Columns in NT vs CRL tabulation

Column	Content
A	The CRL group
B	The median CRL in each group
C	The number of values tabulated in each CRL group
D	The median NT measurement in mm in each CRL
E	The median NT measurement in MoM values in each CRL group. MoM values are recalculated using the specified estimate of gestational age, where necessary. **αlpha** ensures that chronologically correct median equations are selected when recalculating MoM values.

Since there may be systematic differences in NT measurement between sonographers, it is important to specify sonographer-specific or centre-specific NT medians for those sonographers, or groups of sonographers at the same centre, who have made a sufficiently large number of NT measurements (say, at least 100-200 measurements). This helps to reduce the variance of NT MoM values, leading to an improvement in screening performance.49 Sonographer-specific NT medians may be derived by limiting the tabulation to one sonographer (or group of sonographers) using the **Include selected sonographers** option in the **Tabulation** screen (see section 5.13.2). The estimated standard deviation of the $\log_{10}$ NT MoM derived from the tabulations can be compared with published estimates *(see Appendix* J *Statistical parameters: Down's syndrome)* as an indication of whether the measurements of an individual sonographer (or group of sonographers) are suitable for use in screening.

Further information on sonographer specific medians can be found in Sections 5.6 and 6.3.2.

Press the **Print** button for a printed copy of the tabulation or the **Regression** button for a regression of the tabulated data. The regression provides the coefficients needed to update the median equations, should you wish to do this *(see Section 5.9 for more information on regressions)*.

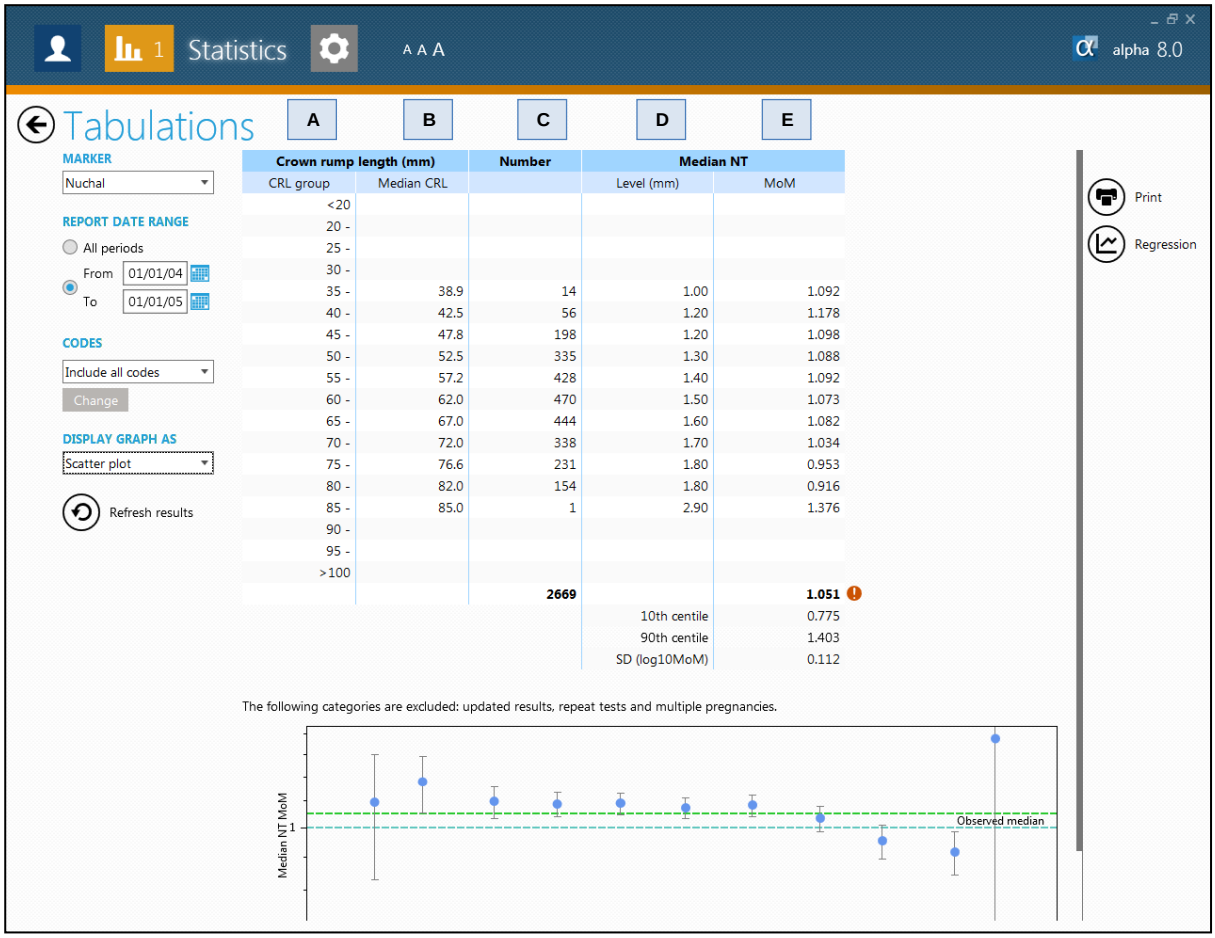

Figure 117: Nuchal translucency tabulation

5.13.5 Tabulation by weight

The **Tabulations** screen provides tabulations according to maternal weight for maternal serum marker MoM values.

You can choose whether to tabulate maternal weight in kilograms or in pounds. As with tabulations by gestational age, you can tabulate data for specified ethnic groups, and you can specify doctors, addresses or sonographers to include or exclude from the tabulation. You can also specify a date range over which to tabulate the data.

Press the **Refresh** button to begin the tabulation. **αlpha** displays a preview of the tabulation, as shown in Figure 118.

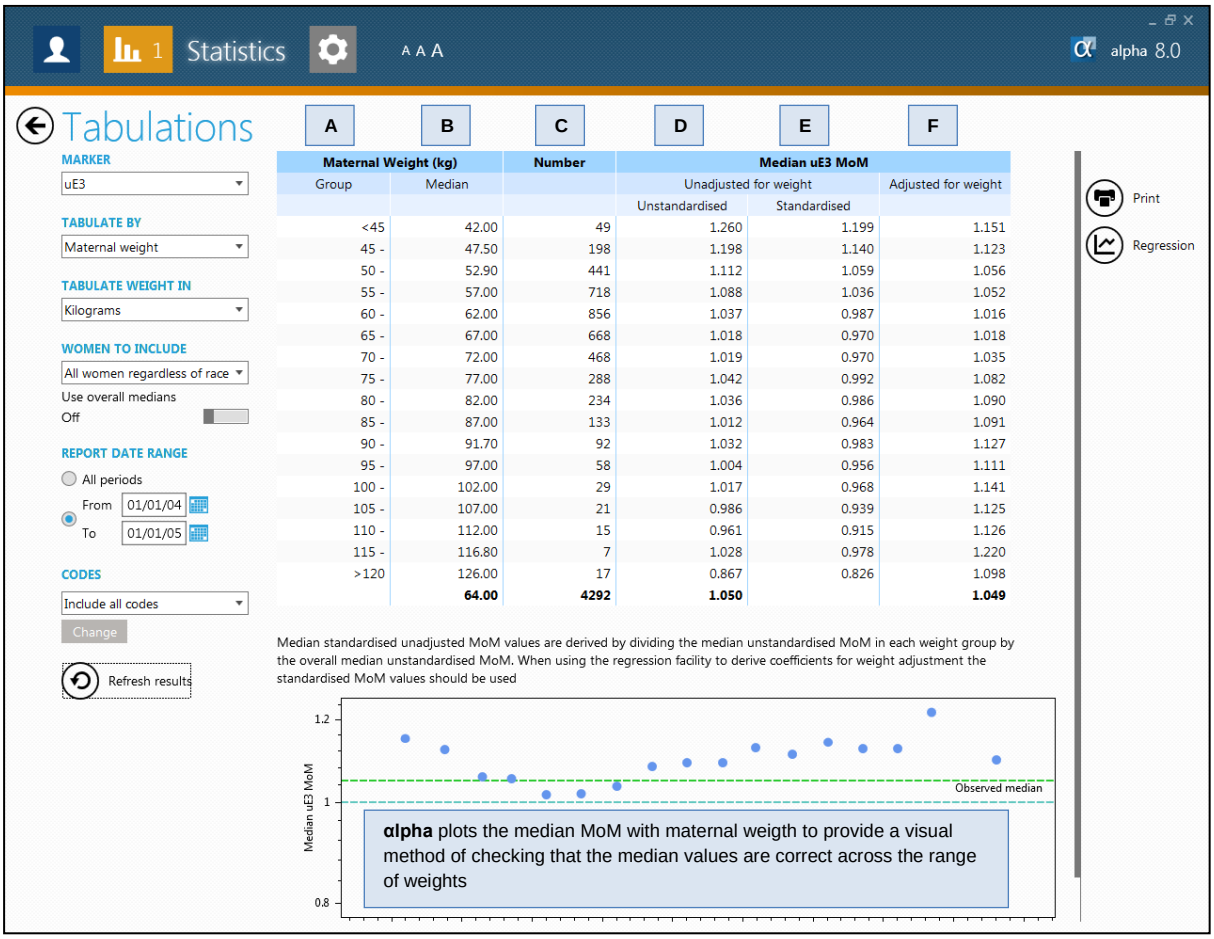

Figure 118: Weight tabulation

There are six columns in the tabulation and these are labelled **A** to **F** in Figure 118 and described in Table 14.

Table 14: Columns in weight tabulation

Column	Content
A	The weight in either 5 kg or 10 pound weight groups.
B	The median weight in each group
C	The number of measurements in each group
D	The median unstandardised MoM in each group
E	The median standardised MoM in each group. The standardised MoM values are derived by dividing the unstandardised MoM values by the overall unstandardised median MoM to correct for any systematic shift in unadjusted MoM values
F	The MoM values adjusted for weight in each group

The expected adjusted median value for each weight group is 1.0 MoM. The unadjusted MoM values will tend to be high in lighter women (>1.0 MoM) and low in heavier women (<1.0 MoM). This is because the volume of interstitial fluid increases with maternal weight, and this will influence the concentration of maternal serum markers [29]. The overall medians for adjusted and unadjusted MoM values should both be close to 1.0 MoM, the aim of weight correction being to adjust each MoM to be the equivalent value for a woman of the median weight in the screened population. Patterns of deviation in the adjusted MoM values, such as being consistently high or low or starting high and ending low, or vice versa, would indicate that the weight adjustment coefficients should be recalculated.

Press the **Print** button for a printed copy of the tabulation or the **Regression** button for a regression of the tabulated data. The regression provides the coefficients needed to update the median equations, should you wish to do this *(see Section 5.9.2 for more information on weight regressions)*.

5.13.6 Serum markers and ethnic groups

Provided your maternal serum (MS) screen design includes the **Ethnic group** prompt, when you tabulate the levels of an MS marker with gestational age or with maternal weight, you can choose to tabulate data either for a specified ethnic group, or for all women, regardless of ethnic group. This section explains why this option is provided, and how **αlpha** tabulates the data in each case.
NOTE: You can change the term **αlpha** uses to refer to 'ethnic group' if you prefer *(see section 3.17).* You can also change the names **αlpha** uses for individual ethnic groups *(see section 3.8)*.

Levels of the serum screening markers may differ, on average, in women of different ethnic groups. Also, average maternal weight may differ between ethnic groups. For example, second trimester AFP levels tend to be higher in black women than in Caucasian women, and South Asian women tend to be lighter than Caucasian women. Correcting for these differences can yield a small but worthwhile improvement in screening performance, as well as helping to ensure a similar screen positive rate in different ethnic groups. [23] If your screened population is ethnically mixed, you may wish to correct for these differences, and **αlpha** allows you to do this in one of two ways.

For each screening marker and each ethnic group, you can choose either the 'direct' method or the 'adjustment' method to allow for differences between ethnic groups *(see section 3.1.3)*. If you choose the direct method for a given marker and a given ethnic group, **αlpha** uses median and weight correction equations that are specific to that ethnic group to convert marker levels in women of that ethnic group into MoM values. If, on the other hand, you choose the adjustment method, then you need to specify a 'reference' group and two correction factors. **αlpha** uses the reference group's median equation and weight correction equation to derive the MoM value in the first instance. It then uses the first correction factor to correct the MoM value for differences in marker levels between the specified ethnic group and the reference group. Lastly, **αlpha** uses the second correction factor to further correct the MoM value for differences in weight between the specified ethnic group and the reference group.

It is appropriate to use the direct method for a given ethnic group when the screened population contains a sufficiently large number of women who belong to that group to allow you to derive and maintain ethnic group-specific medians and weight correction equations. The adjustment method is more suitable for ethnic groups that are represented in smaller numbers in the screened population. For example, if you screen 5,000 women per year, of whom 3,000 are Caucasian, 1,500 are black, and 500 are South Asian, you might reasonably decide to use the direct method for Caucasian and black women. For South Asian women, the small number screened may make it difficult to obtain reliable estimates of the median marker levels, especially over short periods of time.
In this case, it might be preferable to use the adjustment method, specifying the largest ethnic group (Caucasian women) as the reference group, and providing correction factors to allow for differences in marker levels and weight between South Asian and Caucasian women.

A special case is the 'overall' group. This does not correspond to a real ethnic group, but to the screened population as a whole. Medians and weight correction equations for the overall group are derived by tabulating data for all women, regardless of ethnic group. In screening centres with an ethnically homogeneous population, medians and weight correction equations need only be specified for the overall group. Even if the population is ethnically mixed, you still need to provide medians and weight correction equations for this group, since these equations are used to convert marker levels to MoM values in women whose ethnic group is not recorded. The direct method is always used for the overall group, and you cannot specify the overall group as a reference group.

When tabulating serum marker data for an ethnic group that is a reference group for other groups, corrected marker levels from the other ethnic groups will be pooled with the levels from the tabulated group.

Referring to the screened population in the example above, selecting **Caucasian** in the **Tabulation** screen would result in a tabulation comprising data from all Caucasian women, as well as data from South Asian women corrected using the adjustment factor you specified. Median marker levels derived from the tabulation could be used to calculate MoM values in Caucasian and (after adjustment) in South Asian women.

Selecting **South Asian** in the **Tabulation** screen would give a tabulation comprising data from South Asian women only. If your screening policy were to change, such that the 'direct' method was used in South Asian women (for example, because the volume of screening tests increases to the point where a sufficiently large number of South Asian women are screened), you could use the tabulation to derive initial medians for South Asian women.

Selecting **All women, regardless of ethnic group** in the **Tabulation** screen would result in a tabulation comprising data from eligible screening tests in women of all ethnic groups, as well as in women whose ethnic origin was not specified. Median marker levels derived from a regression of the tabulated data could then be used to calculate MoM values in women whose ethnic group is not specified (the 'overall' group). If the checkbox **Use overall medians** is selected in the **Tabulation** screen, the MoM values shown in the tabulation will be based on the medians for the "overall" group. This provides a method of checking the accuracy of the "overall" group medians. If the checkbox **Use overall medians** is not selected in the **Tabulation options** scfeen, the MoM values shown in the tabulation will be based on the medians for each ethnic group. This provides a method of checking how accurate the individual ethnic group medians are.

6 Monitoring your Screening Programme

It is important to monitor your screening programme on a regular basis, especially to ensure that the normal median equations accurately reflect the median levels of the screening markers at different gestational ages for your population. This chapter provides you with helpful notes on some of the routine monitoring tasks you need to perform when using **αlpha**.

6.1 Monitoring Usage

It is often useful to know how many reports have been provided in any given time period. This is easy to determine using the **Report Summary** options *(See Section 5.10).* **Report Summary** provides tables of first tests, updated tests, and repeated tests for both MS and AF over a specified time period. The first test tables are subdivided into the number of reports with each type of screening or diagnostic result (positive, negative, ambiguous or uninterpretable) with further subdivisions indicating the reasons for positive, ambiguous or uninterpretable tests. The update and repeat test tables allow you to monitor the number of tests being updated or repeated, and also to see to what extent screening results are being reclassified following updates and repeat tests.

In addition to using **Report Summary**, you can use **Missing Information** *(section 5.5)* to determine the number of reports requested from each report address. However, this will only be informative if you have selected **Report address** as one of the prompts.

To determine the distribution of reports by gestational week, tabulate a maternal serum marker or AF-AFP by gestation, and the number of reports at each week will be displayed. *(section 5.13.3)*

6.2 Monitoring the False Positive Rate

The screen positive rate is a close approximation to the false-positive rate, since true positives are relatively rare. To determine your screen positive rate, you can use either the **Report summary** table *(See Section 5.10)* or the **Risk Analysis** *(See Section 5.11)*. The report summary will tell you what percentage of reports were initially classified as positive. In addition, the tables of updates and repeats allow you to calculate a final positive rate after reclassification. The Risk Analysis can, in addition, be used to select a Down's risk cut-off that will achieve a specified screen positive rate.

The expected Down's syndrome false-positive rate given the age distribution of screened women is obtained by tabulating the **Screening Performance** *(See section 5.11)*. If the observed screen positive rate is markedly different from the expected false-positive rate, you should, in the first instance, check that the observed medians at each week of gestation are reasonably close to 1.0 MoM. Use **Median Analysis** *(section 5.4)* and the **Tabulation** options *(section 5.2)* to check these.

For markers in which low values are associated with Down's syndrome (for example, AFP, uE_3 and PAPP-A), persistently low observed median MoM values will lead to an increase in screen positive rate. Similarly, for markers in which high values are associated with Down's syndrome (for example, hCG, inhibin-A and nuchal translucency), persistently high observed median MoM values will lead to an increase in screen positive rate.

6.3 Checking and updating the median MoM Values

6.3.1 Monitoring estimate median MoM Values

You should regularly examine observed median MoM values. How often you do this will depend partly on the number of tests you perform, but you should check them at least every three months. The **Median Analysis** option is useful in obtaining a long term picture of fluctuations in reported MoM values *(section 5.4)*

To examine the medians, use the options for tabulation with gestation (or crown-rump length) on the **Tabulations** screen *(section 5.2)*. The tabulations show the observed median MoM at each week of gestation or crown-rump length interval, and the overall median MoM. In expectation, the median MoM is 1.0 for each week or crown-rump length interval, and also overall. The tabulation will indicate whether the overall MoM value lies outside the 95% confidence interval around 1.0 MoM. There may be some fluctuation, and you should not place too much emphasis on median MoM values which are based on small numbers of observations, as is frequently the case for earlier or later gestational ages.

Look for patterns in the median MoM values by week or crown-rump length interval. Consistently high or low values, or trends from high to low or vice versa, will need some attention. If you need to recalculate the median equations, use the **Regression** option and update the coefficients in the usual manner *(section 5.9)*. Remember to use the **Evaluate coefficients** option to examine the new expected medians as a safety check *(see section 3.2.4)*.

You should examine the tabulations for each screening marker and for AF-AFP, as appropriate. If separate median equations are used for women of different ethnic groups you will need to examine the tabulations for each ethnic group, as well as for the overall population.

If separate median equations are used for gestation estimated by scan and gestation estimated by other means, you will need to examine the tabulations using scan-based and dates-based estimates of GA.

When you tabulate the data you should choose a suitable time period. Too long a period, for example, a year, may mask recent changes in median levels, whereas too short a period, for example, a month, may provide insufficient data to truly represent the long term picture. One solution is to tabulate for both the previous month and previous three months. Comparison of these should provide some idea of stability in the median MoM values. The Median Analysis option provides a quick way to in which to do this.

6.3.2 Specifying Sonographer Specific Medians for Nuchal Translucency

There may be systematic differences in nuchal translucency (NT) measurement made by different sonographers. With **αlpha**, you can allow for these differences by specifying sonographer-specific normal medians for NT. Doing so removes a source of variability in NT measurement, 'tightening' the overlapping distributions of NT MoM values in affected and unaffected pregnancies, and leading to improved screening performance.[49]

If you interpret screening tests that include NT (for example, the **Combined Test** or the **Integrated Test**), you should include the **Sonographer** field in your MS screen design (for the Integrated Test, you must include this field). This field can then be used to identify the sonographer who makes each NT measurement (in the case of the Integrated Test, the sonographer must be identified). Even if you do not use sonographer-specific medians, you should record the identity of the sonographer. Doing so will mean that you can monitor NT measurements according to sonographer. *See sections 5.2 and 5.13.4 for further information.* Sonographers are identified by means of sonographer codes *(see section 3.18)*.

When you begin using NT measurement as a screening marker in **αlpha**, you need to specify the coefficients of at least one equation that **αlpha** will use to estimate the expected median NT measurement for a given crown-rump length (CRL) measurement. Such equations should be derived from a regression of historical NT and CRL measurements made by the sonographer(s) who will provide NT measurements in your screening service. Each regression should be based on at least 100 NT and CRL measurements, preferably evenly distributed across at least three gestational weeks (between 10 and 13 weeks).

For individual sonographers who have made at least 100 NT and CRL measurements, it may be possible to derive sonographer-specific regressions. Tabulate each sonographer's NT and CRL measurements *(as described in section 5.13.4)* and examine the regressions obtained. Provided the regressions fit the observed median NT values reasonably well, and the rates of increase of NT are as expected (about 15%-25% per gestational week) you may decide to specify sonographer-specific medians for those sonographers. To do so, first print a copy of the regression, and then select the **Coefficients** option on the **System** menu. Click **NT & CRL,** then click **Add sonographer** and then select the sonographer from the list. Enter the coefficients (A and B) from the printed regression, and click **Add** to assign those coefficients to the selected sonographer.

If there are too few historical measurements initially to provide sonographer-specific regressions, a reasonable approach would be to pool the measurements from all sonographers in a single regression, and assign the coefficients of the regression equation to the **Overall** NT medians. To do so, first print a copy of the regression, and then select the **Coefficients** option on the **System** menu. Double click **NT & CRL,** then double click **Overall** and enter the coefficients A and B from the regression. Once a sufficiently large number of NT measurements have been made by individual sonographers, sonographer-specific medians could be specified.

As time progresses, and you accumulate NT measurements in your **αlpha** database, you can monitor each sonographer's measurements individually using **Median Analysis** *(see section 5.4)* and **Tabulations** *(see section 5.13.4)*. Use these facilities to identify systematic differences in NT measurement between sonographers, and potential problems in NT measurement (for example, rates of increase that fall outside the expected range of 15%-25% per week, or standard deviations that differ markedly from published estimates).

6.4 Changing Assays

If you intend to change an assay, you will need to establish normal medians for the new assay, by assaying a sufficiently large number of routine samples in parallel with the old assay. Preferably, the new medians will be based on at least 50 samples per week in four gestational weeks.

Use the **Regression** option to calculate median equation coefficients for the new assay. On the day you wish to start interpreting results using the new assay, add the new coefficients in the **Coefficients** section. You may also need to change the concentration units in the **Parameters** section.

When you are tabulating data in **αlpha** you will need to remember when you changed to a new assay; a historical listing of the coefficients will indicate the dates when the normal medians were changed. You can examine tabulated median MoM values over different assays, as **αlpha** always uses the correct median equation when calculating the MoM values. However, care should be taken when examining the combined unit values for more than one assay, as they will probably not be suitable for deriving new median equations. **αlpha** allows you to restrict the tabulations to specified date ranges, so you can avoid tabulating data from more than one assay.

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Appendix A Rules used in producing reports

A report may contain various items of information which are derived from a combination of the input data and the appropriate parameter and coefficient settings. The main rules and considerations affecting this are outlined here.

Gestational age (GA) by Dates

1. If LMP and EDD estimated from LMP are both recorded, LMP is used.
2. If LMP/EDD and GA by dates are both recorded, the gestation derived from LMP/EDD is used.
3. If the month of LMP or EDD is known but not the day of the month, the 15th day is used in calculations.

Gestational age (GA) by Scan

1. If fetal measurement(s) (biparietal diameter [BPD], crown-rump length [CRL] or abdominal circumference [AC]) and GA by scan are both recorded, the gestation derived from the fetal measurement(s) is used.
2. Fetal measurement(s) and GA estimated by scan take precedence over EDD estimated by scan.
3. In a twin pregnancy, if two fetus-specific BPD, CRL, AC or HC measurements are recorded, the mean of the corresponding gestations is used in calculating the MoM values for serum markers. For ultrasound markers, such as nuchal translucency, a separate MoM value is calculated for each fetus, based on the corresponding fetus-specific CRL measurement (or estimated CRL measurement where CRL is not recorded).

Gestational age (GA) by crown-rump length (CRL)

In screening tests that include the measurement of nuchal translucency (NT), a CRL measurement will normally have been made at the same ultrasound examination. This is the preferred approach, since the NT MoM value may then be based directly on the CRL at the time of NT measurement. In cases where a CRL measurement is not made in the same ultrasound examination, the NT MoM is based on an indirect estimate of CRL derived according to the following rules:-

1. If no CRL measurement is available, the CRL corresponding to the best alternative estimate of gestational age (other ultrasound measurement, if available, 'dates' otherwise) is estimated from the equation (derived from [77])

   CRL (mm) = $(0.1223 \times \text{gestational age (days)} - 2.8046)^2$

2. If a CRL measurement is available, but was made on a different date from the NT measurement, the CRL corresponding to the date of NT is estimated from the equation used to estimate gestational age for a given CRL measurement *(see Section* 3.2.1.3 *Equations used to estimate gestational age from fetal ultrasound measurements)*.

As stated above, the preferred approach is to record an NT and a CRL measurement made at the same time. **αlpha** includes such NT measurements in tabulations of NT with CRL, and therefore they contribute to the monitoring of NT measurement. Exceptionally, if no CRL measurement is available, or if the CRL is measured at a different time from the NT, alternative estimates may be used, however, such NT measurements are excluded from tabulations, and monitoring of NT measurement will be incomplete.

Gestational age (GA) by Clinical
This is taken to be the recorded number of completed weeks plus three days.

Precedence among GA estimates
If more than one estimate of gestation is available the one adopted is determined by the purpose for which the estimate is to be used. The following table shows the order of precedence for different uses:

Use		Gestational age based on				
		BPD	**CRL**	**Other Ultrasound Measure**	**Dates**	**Clinical**
Screening markers						
1	Acceptable time for test *	2	1	2	3	4
2	Maternal age at EDD	2	1	2	3	4
3	MoM calculation ** (Down's syndrome Screening)	2	1	2	3	4
4	MoM calculation ** † (open NTD Screening)	1	2	2	3	4
AF-AFP						
1	Acceptable time for test *	1	1	1	2	3
2	MoM calculation and cut-off selection:					
	a) BPD gestation less than dates	3	1	1	2	4
	b) Otherwise	1	1	1	2	3

* *Those tested too early are rescheduled to return at 16 weeks (for second trimester screening) or 10 weeks (for first trimester screening), using same priority*

** *and consequently the type of parameter used for risk calculation*

† *If MoM values based on BPD and CRL measurements both lie on the same side of the AFP cut-off, only the CRL-based MoM is reported. If they lie on opposite sides of the cut-off, both are reported, and a comment is added to the report indicating that the BPD-based MoM was used for spina bifida screening* [56]

Maternal age

If age at EDD and date of birth are both given, date of birth is used. Where maternal age at EDD is calculated as less than 15 years, the age-specific risk at 15 years is used.

Maternal serum marker MoM value

Adjustment is made for maternal weight when available.

Positive Screening Result

At least one of:

i) MS-AFP MoM value ≥ cut-off (in twins and diabetics, adjusted MS-AFP MoM value ≥ cut-off)
ii) risk of Down's ≥ cut-off (in twins, risk of Down's probably ≥ cut-off)
iii) previous NTD pregnancy (provided gestational age ≥ 15 weeks)
iv) previous Down's syndrome pregnancy
v) If interpretation for pre-eclampsia requested, risk of pre-eclampsia ≥ cut-off
vi) If interpretation for pre-eclampsia requested, previous pregnancy affected with pre-eclampsia

Positive Diagnostic Result

One of:

i) AF-AFP MoM value ≥ GA-specific cut-off and AchE test not done
ii) AF-AFP MoM value ≥ GA-specific cut-off and AchE NTD band present

Ambiguous Diagnostic Result

One of:

i) AF-AFP MoM value ≥ GA-specific cut-off and AchE NTD band absent
ii) AF-AFP MoM value < GA-specific cut-off and AchE NTD band present

Uninterpretable Screening Result

At least one of:

i) in second trimester screening for Down's syndrome, GA < 14 weeks 0 days or > 22 weeks 6 days [1]
ii) in first trimester screening for Down's syndrome, GA < 10 weeks 0 days or > 13 weeks 6 days
iii) in integrated screening for Down's syndrome, GA at first sample < 10 weeks 0 days or > 13 weeks 6 days, and GA at second sample < 14 weeks 0 days or > 22 weeks 6 days [1]
iv) in screening for open NTD, GA < 15 weeks 0 days or > 22 weeks 6 days [1]
v) triplets or more fetuses
vi) an amniocentesis has been attempted during pregnancy prior to the sample date

Uninterpretable Diagnostic Result

One of [2]:

i) GA < 13 weeks 0 days
ii) GA > 24 weeks 6 days

[1] Or the MS 2nd trimester interpretation range selected (see *Appendix C Acceptable settings for parameters*)
[2] Or the AF-AFP interpretation range selected (see *Appendix C Acceptable settings for parameters*)

Risk Estimates

1 If a BPD is recorded, anencephaly can be excluded and the risk of open NTD given is for spina bifida only.

2 In second trimester screening, if the test is a repeat, maternal serum MoM values from both the test being reported and the previous test are used to estimate the risk, provided
i) both results are interpretable *and*
ii) the second MoM value is not more than twice or less than half the first MoM value, for each marker. If the second MoM is not within this range a message is printed on the report.

3 If there is a previous Down's syndrome pregnancy with an inherited translocation, it is taken to be a non-homologous maternal translocation.

4 If there is a previous Down's syndrome pregnancy of unknown type, it is taken to be non-inherited.

5 MS-AFP, uE_3, hCG (first and second trimester), NT and PAPP-A MoM values are used, where available, to estimate the risk of trisomy 18. MS-AFP, uE_3, and total hCG MoM values are used, where available, to estimate the risk of and Smith-Lemli-Opitz syndrome (SLOS). Inhibin, NT, hCG and PAPP-A MoM values are used to estimate the risk of trisomy 13.

6 Risks are rounded as follows:

1 in 20 – 1 in 99	to the nearest 5;
1 in 100 – 1 in 999	to the nearest 10;
1 in 1,000 – 1 in 9,999	to the nearest 100;
1 in 10,000 – 1 in 99,999	to the nearest 1,000;
1 in 100,000 – 1 in 999,999	to the nearest 10,000.

7 Risk estimates higher than a specified value *x in y* are reported as greater than x in y. *(See Section 3.1.10* Printing of risks for *acceptable values for x and y).*

8 Risk estimates lower than a specified value 1 in *x* are reported as less than 1 in x. *(See Section 3.1.10* Printing of risks for *acceptable values for x and y).*

Parameters and Coefficients

When more than one setting is available for a parameter or coefficient, the chronologically correct setting is used. The date the report is produced is used when selecting the correct setting, except where the date of assay is specified, when the date of assay is used instead. When more than one setting is available for the date of report or date of assay, the later setting is used. For corrected or updated reports, the settings on the date of the original report are used.

Repeat Tests

Clinical information, including gestational age, maternal weight, date of previous amniocentesis, previous Down's syndrome or NTD pregnancy, and diabetes from an earlier report may be used in producing the repeat test report. Where there is a discrepancy between the information provided with the earlier test and the later test, priority is given to the most recent information.

Appendix B Prompts and their meanings

Prompt	Maximum characters	Meaning of input and notes
Surname	50	Patient's surname. May be omitted if both **ID Code** and **Date of birth** are included
Forename(s)	50	Patient's forename(s). If initials are entered they should be separated by a space or '.'
ID Code [a]	50	A patient-specific or pregnancy-specific identification code Sample-specific codes (e.g. lab numbers, specimen numbers) must **not** be used in this field, since it is used in identifying potential repeat samples in the same pregnancy. **ID Code** may also be used to identify records relating to screening in a previous pregnancy, to help avoid recurrent false-positives (*see Section* 3.1.11). If your policy is to match such records (strict matching or loose matching) the ID Code must be patient-specific (**not** pregnancy specific) May be omitted if both **Surname** and **Date of birth** are included
Address 1 Address 2 Address 3	50 50 50	Patient's address
Postcode	10	Patient's postcode
Phone number	15	Patient's telephone number
Doctor	50	Doctor's name in full, or a code (up to 8 letters or numbers for 50-character name). Include this field if you want doctor-specific summaries and statistical tabulations. If included, **Reports To** must be omitted
Report Address	8	Alphanumeric code for address to send report (codes for up to 4 lines of 50 characters). Include this field if you want centre-specific summaries and statistical tabulations. If included, **Reports To** must be omitted
Reports to	N/A	Displays a pop-up window in which the names (or codes) for up to three doctors can be entered, together with their report address codes. One copy of the final report is printed and addressed to each doctor. The language for each report may also be specified. If included, **Doctor** and **Report Address** must be omitted
Date of Birth	3 x 2	Patient's date of birth. May be omitted if **ID Code**, **Surname** and **Age at EDD** are included
Age at EDD	2	Maternal age at expected date of delivery. This field is only used when **Date of Birth** is not known. In such cases, **αlpha** assumes the mid-point of the specified year of age (for example, if 35 is entered, 35.5 years in used in calculations)

Gestational age estimation (dates)		
LMP	3 x 2	First day of last menstrual period (LMP). If the exact date is not known, enter 00 for the day of the month (e.g. 00/12/2005).In such cases, **αlpha** uses the 15th day in calculations.
EDD from LMP	3 x 2	Expected date of delivery based on LMP
Certain	1	1 = LMP/EDD certain 2 = LMP/EDD doubtful If chosen, the field must follow 'LMP' and/or 'EDD from LMP'. Women whose LMP is recorded as being doubtful may be excluded from certain statistical tabulations
GA by Dates [b]	4	Estimated gestational age based on LMP, in completed weeks and days (separated by ',' or '+')
On	3 x 2	Date to which **GA by Dates** relates. Required if **GA by Dates** is given

Gestational age estimation (ultrasound)		
EDD from scan [a]	3 x 2	Expected date of delivery based on ultrasound scan
GA by scan [b]	4	Estimated gestational age based on ultrasound scan, in completed weeks and days of gestation (separated by ',' or '+')
On	3 x 2	Date to which **GA by scan** relates. Required if **GA by scan** is given
Number of fetuses	1	Number seen at scan. If left blank, **αlpha** assumes a singleton pregnancy
Scan measure	1	1 = BPD in singleton fetus 2 = one BPD in twins 3 = both BPDs in twins 4 = other 5 = not known Required if **GA by scan** is given. If **Number of fetuses** is blank or 1, options 2 and 3 are not allowed. If **Number of fetuses** is 2, option 1 is not allowed
Date of scan [b]	3 x 2	Date of ultrasound scan This prompt, together with the following five linked prompts, must be included in the screen design if you wish to interpret the **Integrated Test**
Machine [a]	1	Code (between 1 and 9) identifying the ultrasound machine (or type of machine) used to perform the examination, or the centre at which the examination is performed. The code is used to select a machine- or centre-specific equation for estimating GA from ultrasound measurements. In addition, if the **Type of Measure** is 1 (BPD), it is used to select the appropriate BPD correction factor for the machine or type of machine *(see Section 3.1.5)* Required if **Date of scan** is given
Number of fetuses	1	Number seen at scan If left blank, **αlpha** assumes a singleton pregnancy

Type of Measure	1	1 = BPD 2 = CRL 3 = AC 4 = HC Required if **Date of scan** is given
Measurement (1) [e]	5	Measurement (mm) on date of scan Required if **Date of scan** is given
Measurement (2)[e]	5	Second measurement if multiple pregnancy Not available if **Number of fetuses** is blank or 1 Optional if **Number of fetuses** is 2
Type of Measure [b,a]	1	1 = BPD 2 = CRL 3 = AC Optional second ultrasound measurement (**Date of scan** is taken to be the same for both measurements**)**
Measurement (1) [e,a]	5	Measurement (mm) on date of scan Required if **Type of measure** is given
Measurement (2) [e,a]	5	Second measurement if multiple pregnancy Not available if **Number of fetuses** is blank or 1 Optional if **Number of fetuses** is 2

Gestational age estimation (clinical)

GA by clinical [b]	2	Estimated gestational age based on clinical examination in completed weeks only Women in whom **GA by clinical** is the only available estimate of GA are excluded from certain tabulations
On	3 x 2	Date to which **GA by clinical** relates

Screening (MS) related information

First or repeat [f]	1	1 = first screening sample this pregnancy 2 = repeat sample If this field is used to indicate a repeat sample, and the record is not subsequently matched to an earlier record relating to a previous sample in the same pregnancy, a message to this effect appears on the report
Weight [e]	5	Woman's weight The units (kilograms or pounds) may be specified in **Weight units**, if it is included in the screen design. If not, or if **Weight units** is left blank, the units are taken from the parameter settings *(see Section 3.1.13)*
Weight units	1	0 = kilograms 1 = pounds If given, the value entered overrides the default weight units specified in the parameter settings *(see Section 3.1.13)*
Date weighed	3 x 2	If chosen this prompt should follow **Weight** Not used in the interpretation

Previous Down's	1	0 = none 1 = non-inherited 2 = inherited translocation 3 = type unknown Type of previous pregnancy (if any) affected with Down's syndrome. If 3 (type unknown) is entered, 1 (non-inherited) is assumed by default. When a previous affected pregnancy is recorded, a recurrence risk of 0.34% (if non-inherited) or 10% (if inherited) is added to the age-specific risk at term [9]. In addition, the result is classified as screen-positive, regardless of the levels of the screening markers. MoM values from any previous pregnancy will not be taken into account *(see Section 3.1.11 for further information)*
Age at previous pregnancy	2	Not available if **Previous Down's** is **none.** If known, the age at which a previous pregnancy was affected with Down's syndrome is used to calculate the Down's syndrome recurrence risk above the maternal age-related risk[61]. If left blank, the adjustment described in **Previous Down's** is made.
Previous NTD	1	0 = none 1 = one 2 = two or more Number of previous pregnancies (if any) affected with open NTD. If a previous affected pregnancy is recorded, the result is classified as screen-positive, regardless of the AFP level. In the case of a single previous pregnancy affected with NTD Alpha will multiply the NTD prevalence by ten if the total NTD prevalence is 0.005 or more and by 15 if less than 0.005. For two or more previous pregnancies affected with NTD the resulting prevalences are doubled.[95]
Diabetes	1	0 = none 1 = insulin-dependent diabetes mellitus In women with insulin-dependent diabetes mellitus, MoM values of serum markers may adjusted before being used in the interpretation. If left blank, patient is assumed to not be diabetic. *See Section Appendix P Factors used for adjusting MoM values for more information.*
Ethnic group [g]	1	1 = black 2 = non-black 3 = not known 4 = group 4 5 = group 5 6 = group 6 If this prompt is included in the screen, the ethnic group entered is used to select ethnic group-specific median equations and weight correction equations *(see section 5.13.6 for more information)*. In addition, ethnic group-specific prevalences for spina bifida, anencephaly and pre-eclampsia are selected *(see Section 3.1.4 for more information)*.

Date of sample	3 x 2	Date blood sample taken. Dates earlier than 280 days before the current date are not accepted
Date of second sample	3 x 2	Date second blood sample taken (integrated screening only). Dates earlier than 280 days before the current date are not accepted
Previous amnio	3 x 2	Date of last amniocentesis performed or attempted in this pregnancy. The result is uninterpretable if an amniocentesis has been performed or attempted. This is because amniocentesis sometimes causes feto-maternal transfusion which can increase the maternal serum AFP level
Interpretation	1	1 = Down's syndrome and NTD 2 = NTD only 3 = Down's syndrome only 4 = Down's syndrome, NTD and pre-eclampsia 5 = Down's syndrome and pre-eclampsia Specifies the type of interpretation required. If left blank, an interpretation is provided for Down's syndrome and NTD, except for second trimester tests performed at 14 weeks, and first trimester tests, when the interpretation is for Down's syndrome only. Interpretations for pre-eclampsia are only given for second trimester tests.
Amniotic sacs	1	The number of amniotic sacs in a twin pregnancy. Not used in the interpretation.
Chorionic sacs	1	The number of chorionic sacs in a twin pregnancy Used as an indication of zygosity in screening tests that include **NT** measurement Dichorionic twins are assumed to be dizygous. Monochorionic twins are taken to be monozygous. If left blank, the pregnancy is assumed to be dichorionic.[48,57]
Integrated Screening	1	0=No 1=Standard integrated (Combining the results of the first and second trimester markers) 2=Sequential testing (Only women who have a negative first trimester test proceed to the full Integrated test) This field must be included in the screen design if you wish to interpret the **Integrated Test**. If included, the type of test (Integrated or standard Integrated or Sequential testing) must be specified for each woman screened. This field should preferably precede **Date of sample** and **Date of second sample** in the screen design
Sonographer	8	Code (up to 8 letters or numbers) identifying the sonographer who made the nuchal translucency (NT) measurement. Required in Integrated Tests which include NT
Smoker	1	0=No 1=Yes **αlpha** adjusts MoM values of certain serum markers in smokers to allow for differences in the levels between smokers and non-smokers. If left blank patient is assumed to be a non-smoker. *See Section Appendix* P *Factors used for adjusting MoM values for more information)*

IVF pregnancy	1	0=No 1=Yes **αlpha** adjusts MoM values of certain serum markers in IVF pregnancies to allow for differences in the levels between IVF and naturally conceived pregnancies. If left blank it is assumed to not be an IVF pregnancy. See Factors used for adjusting MoM values see Appendix P for more information)
Donor date of birth	3 x 2	The donor's date of birth in an IVF pregnancy in which the egg is donated. This is used instead of the pregnant woman's date of birth to determine the age-specific risk of Down's syndrome
Donor age at EDD	2	The donor's age at the estimated date of delivery in an IVF pregnancy in which the egg is donated, and the donor's date of birth is not known. This will be used instead of the pregnant woman's age to determine the age-related risk of Down's syndrome
Date of egg collection	3 x 2	In an IVF pregnancy using a frozen embryo, the date of egg collection (oocyte retrieval). The mother or donor's age at EDD used for the Down's syndrome risk calculation will be her actual age at EDD less the number of days the embryo was frozen which is taken to be the time between the date of embryo transfer and the date of egg collection.
Date of embryo transfer	3 x 2	In an IVF pregnancy, the date of embryo transfer. Gestational age is taken to be 18 days longer than the time since embryo transfer[87]. If the date of embryo transfer is recorded, this takes precedence over other estimates of gestational age. (Prior to version 7.0V this field was called "Date of egg collection")
MS-AFP and uE_3 [c,e]	6	A six digit number or < (less than) followed by a five digit number.
Other serum markers and DVPI [c,e]	7	A seven digit number or < (less than) followed by a six digit number
Nuchal translucency [c.e]	9	A four digit number (or, in a twin pregnancy, two four digit numbers separated by a /)
Assay date (serum markers only)	3x2	Date field appearing after each serum marker. Used in cases where the median or weight correction equations may have changed after the date of assay (for example, those relating to first trimester markers in the Integrated Test). If specified, the assay date is used to select the chronologically correct equations. If left blank, the date of the report is used instead

Date of NT	3x2	Date field appearing after nuchal translucency (NT). Used in cases where NT is not measured in the same ultrasound examination as crown-rump length (CRL), or where CRL was not measured. If specified, the date is used to estimate the CRL measurement corresponding to the date of measurement of NT, for the purpose of calculating the MoM value. The date is also used to specify the chronologically correct equations, If left blank, it is assumed that NT was measured in the same examination as CRL. If CRL was not measured, the date of NT **must** be specified
Nasal bone (fetus 1) [b]	1	0 = absent 1 = present 2 = not reported If absent or present nasal bone is recorded, this is used to adjust the risk of Down's syndrome, using the method of Cicero *et al.* [52] . The nasal bone adjustment is not made when the sample gestational age is less than 11 weeks.
Nasal bone (fetus 2)	1	0 = absent 1 = present 2 = not reported Used to record the absence or presence of nasal bone in the second fetus in a twin pregnancy. Not available for singleton pregnancies.
Previous pre-eclampsia	1	0 = No 1 = Yes When screening for pre-eclampsia and a previous pregnancy has been affected with pre-eclampsia, the result is classified as screen-positive, regardless of the levels of the screening markers. Not used in an interpretation for Down's syndrome or open neural tube defects.
Ductus venosus blood flow	1	0 = Reverse or absent 1 = Forward 2 = Not reported

Amniotic fluid (AF) related information

First or repeat [f]	1	1 = first AF-AFP test this pregnancy 2 = repeat sample If this field is used to indicate a repeat sample, and the record is not subsequently matched to an earlier record relating to a previous sample in the same pregnancy, a message to this effect appears on the report
Diabetes	1	0 = none 1 = insulin dependent diabetes mellitus Not used in the interpretation
Ethnic group [g]	1	1 = black 2 = non-black 3 = not known 4 = group 4 5 = group 5 6 = group 6 Not used in the interpretation

Previous NTD	1	0 = none 1 = one 2 = two or more Not used in the interpretation
Amnio reason	1	1 = raised MS-AFP 2 = suspicion of NTD on ultrasound 3 = previous suspicious AF-AFP/AchE 4 = family history of NTD 5 = increased risk of Down's syndrome 6 = unrelated to NTD or Down's risk 7 = advanced maternal age 8 = abnormal ultrasound finding 9 = increased risk of trisomy 18 Not used in the interpretation
AF appearance	1	1 = clear 2 = cloudy 3 = frankly bloodstained 4 = significantly discoloured If the amniotic fluid sample is bloodstained or significantly discoloured, and the diagnostic result is positive (raised AF-AFP) a message is added to the report, indicating that the result may be a false-positive due to blood contamination of the amniotic fluid.
AF-AFP [c,e]	5	A five digit number or < followed by a four digit number
AChE NTD band	1	1 = faint 2 = strong 3 = absent 4 = pending Amniotic fluid acetylcholinesterase (AchE) is one of the two main biochemical diagnostic tests for open NTD (the other is raised AF-AFP). A faint or strong AchE band together with raised AF-AFP indicates a positive diagnostic result. If the band is absent and AF-AFP is not raised, or if the band is present and AF-AFP is raised, the result is classified as ambiguous.
PChE bands	1	1 = single 2 = multiple 3 = absent 4 = pending A combination of an AchE NTD band and multiple PchE bands is consistent with a neural tube defect, abdominal wall defect, intrauterine death or blood contamination of the amniotic fluid, and a message to this effect is added to the report.
Fetal cells (%)	3	Result of AF-Kleihauer test Fetal blood contamination of amniotic fluid can be a cause of false-positive amniotic fluid AFP and AchE results. Not used in the interpretation
RBC (million/ml)	3	Concentration in amniotic fluid Contamination of amniotic fluid with fetal (not maternal) blood can cause AchE false positives, especially if there are more than about 60 million fetal red cells per ml of amniotic fluid. Not used in the interpretation

Other		
Lab number	15	Any string
Spare (1)	50	Any string
Spare (2)	50	Any string
Spare (3)	50	Any string
Spare (4)	50	Any string
Spare (5)	50	Any string
Spare (6)	50	Any string
Femur length (1) [b,d]	3	Measurement (mm) on date of scan Not used in the interpretation.
Femur length (2)	3	Second measurement if multiple pregnancy Not used in the interpretation.
Date received	3 x 2	Date sample reached laboratory Not used in the interpretation.
Time received	4	Hours (2 digits) followed by minutes (2 digits) Not used in the interpretation.
Date 2nd sample received	3 x 2	Date 2nd sample reached laboratory (integrated screening only) Not used in the interpretation.
Time 2nd sample received	4	Hours (2 digits) followed by minutes (2 digits) (integrated screening only) Not used in the interpretation.
Date OC stopped	2 x 2	Month and year patient stopped using oral contraceptives Not used in the interpretation; however, women in whom oral contraceptive use is recorded within 60 days of conception may be excluded from certain tabulations.

(a) These prompts allow a second set of ultrasound measurements to be entered. If chosen they should follow the primary prompts (previous item)

(b) Linked prompts; if the first is chosen, the others are included automatically

(c) The units chosen as parameters *(see Appendix C Acceptable settings for parameters)* are automatically displayed with these prompts

(d) These prompts can only be chosen for maternal serum tests and provided 'Date of scan' and the associated prompts are chosen too

(e) These numbers may contain a decimal point and will be printed on the reports as entered

(f) This prompt is no longer required and is included for compatibility with previous versions of **αlpha**

(g) Alternative names may be given to the six groups if desired. However code 3 is reserved for women of unknown ethnic group and should only be used for this purpose

N.B. Dates (apart from Date OC stopped) are entered as six digits, two each for day, month and year. The order of the day, month and year is determined by your computer's regional settings.

Appendix C Acceptable settings for parameters

Parameter		Acceptable settings
Median equation policies		
MS-AFP, uE3, total hCG, free ß hCG, inhibin-A, PAPP-A,PlGF	For overall population & up to 5 specified ethnic groups	single equation; separate equations for GA by scan and for GA by dates or clinical examination
Adjustment for ethnic group		
MS-AFP, uE3, total hCG, free ß hCG, inhibin-A, PAPP-A,PlGF	For up to 5 specified ethnic groups	Direct method (**αlpha** will expect to find a median equation and a weight correction equation for the specified ethnic group) Adjustment method (in women of the specified ethnic group, αlpha uses the median equation and weight correction equation for a specified reference population, adjusting the MoM value using two correction factors that allow for differences in the normal median and in maternal weight between the specified ethnic group and the reference group). *See section 5.13.6 for further information*
Reinterpretation of screening result		Always reinterpret Reinterpret only if scan and dates GA differ by at least n days (n≤28)
Units		
Maternal serum markers		ng/mL, ug/L, iu/mL, kiu/L, iu/L, nmol/L, miu/mL, pg/mL, mg/L, miu/L
Nuchal translucency		mm
AF-AFP		ug/mL, mg/L, kiu/mL, Miu/L
MAP		mmHg
Maternal weight		kilograms or pounds
Ductus venosus pulsatility index		None
Footnotes		
MS screen positive message MS screen negative message		print, do not print

Printing of risks	
Down's risk (positive) Down's risk (not positive) Prior risk of Down's (positive) Prior risk of Down's (not positive)	never, always, if age ≥ *x* years[1]
Down's risk comparison	never, when positive or age ≥ *x* years[1]
Print trisomy 18 risk	never, when positive, when positive and print comment when negative
Print trisomy 13 risk	never, when positive, when positive and print comment when negative
Print SLOS risk	never, when increased AND Down's or trisomy 18 risk is increased, when increased , when increased and print comment when decreased

Parameter	Acceptable settings
Print NTD risk	never, always, when positive
Timing of Down's risk	
Timing of trisomy 18 risk	term, time of test
Timing of trisomy 13 risk	
Trim printed risk (non-Integrated Tests) [2]	1 in 20000 – 1 in 1000000
Trim printed risk (Integrated Tests) [2]	1 in 20000 – 1 in 1000000
Cap printed Down's risk (first trimester) [2]	4 in 5 – 1 in 5
Cap printed Down's risk (second trimester) [2]	4 in 5 – 1 in 5
Cap printed Down's risk (Integrated Test) [2]	9 in 10 – 1 in 2 for the risk of Down's syndrome in Integrated Test
Cap printed trisomy 18 risk [2]	4 in 5 – 1 in 5
Cap printed NTD risk	4 in 5 – 1 in 5
MS 2nd trimester interpretation range	Range starts from 14 or 15 completed weeks, finishes between 19 and 22 completed weeks
AF-AFP interpretation range	13 to 24 completed weeks or 15 to 21 completed weeks.
Print Riskometer	Yes or No
Print Pre-eclampsia risk	Yes or No (Default setting)
Print Adjusted MoMs	Do not adjust (Default setting) or Adjust
Cut-offs	
Down's risk (second trimester)	
Down's risk (first trimester)	
Down's risk (Integrated Test with NT)	1 in 100 – 1 in 500
Down's risk (Integrated Test without NT)	
Trisomy 18 risk (second trimester)	
Trisomy 18 risk (first trimester)	
Trisomy 18 risk (Integrated Test)	1 in 50 – 1 in 300
Trisomy 13 risk	
SLOS risk	
Sequential testing first trimester risk	1 in 10 – 1 in 60
NTD MS-AFP	2.0 – 4.0 MoM
NTD MS-AFP (diabetics)	2.0 – 4.0 MoM
NTD AF-AFP 13-15 weeks (1)	2.0 – 4.0 MoM
NTD AF-AFP 16-18 weeks (2)	2.0 – 4.5 MoM & ≥ (1)
NTD AF-AFP 19-21 weeks (3)	2.0 – 5.0 MoM & ≥ (2)
NTD AF-AFP 22-24 weeks (4)	2.0 – 5.5 MoM & ≥ (3)
Pre-eclampsia risk	1 in 5 – 1 in 300

Background prevalences for overall population and up to 5 specified ethnic groups	
Spina bifida Anencephaly	0.2 – 4.0 per 1000
Pre-eclampsia	10 – 80 per 1000
BPD correction factors	
Ultrasound machine 1-9	1540 m/s outer to inner edge of cranium 1540 m/s outer to outer edge of cranium 1600 m/s outer to inner edge of cranium 1600 m/s outer to outer edge of cranium
AF-AFP median reduction factors	
13 completed weeks	0-40% reduction
14 completed weeks	0-20% reduction
Recurrent false positives	Do not adjust, strict matching, loose matching

1 The value of *x* must be specified. Values in the range 12-55 years are accepted

2 See Section 3.1.10

Appendix D Equations used in calculations

Median Equations [a]

Marker	Expected median =	Equation type
Second trimester		
MS-AFP	$A \times B^{GA(days)}$	Log linear [70]
uE_3	$A \times B^{GA(days)}$	Log linear [13]
	OR	
	$A + B \times GA(days)$	Linear [70]
	OR	
	$A \times 0.9996379^{(\text{GA (days)}-170.82)\times(\text{GA (days)}-170.82)}$	Log-quadratic [85]
Total hCG	$A + B \times e^{(-0.08268 \times (\text{GA(days)}-100))}$	Exponential [13]
Free ß hCG	$A + B \times e^{(-0.054975 \times (GA(days)-100))}$	Exponential [92]
Inhibin-A	$A \times 1.000429^{((GA(days)-120)\times(GA(days)-120))}$	Log-quadratic [62]
	OR	
	$\log_{10}(inhibin - A) = k + [0.0003838 \times \text{GA(days)}] + [0.0002311 \times (\text{GA(days)} - 120)^2] - [0.000004029 \times (\text{GA(days)} - 120)^3]$	Log-cubic [68 d]
AF-AFP	$A \times B^{GA(days)}$	Log linear [8]
MAP	$A \times B^{GA(days)}$	Log linear [93]
PlGF	$A \times B^{GA(days)}$	Log linear [93]
First trimester		
Total hCG	$A \times B^{GA(days)}$	Log linear [21]
Free ß hCG	$A \times B^{GA\,(days)} \times C^{GA\,(days)\times GA(days)}$	Log-quadratic [21]
PAPP-A	$A \times B^{GA(days)}$	Log linear[21]
Nuchal translucency [c]	$A \times B^{CRL(mm)}$	Log linear [28]
Ductus venosus pulsatility index	Constant	Constant [81]
PlGF	$A \times B^{GA(days)}$	Log linear[91]

Weight Adjustment

Marker	One of the following equations can be chosen.	Equation Type
All markers	$Adjusted\ MoM = \frac{MoM}{A \times B^{Weight(kg)}}$	Log linear [13]
	$Adjusted\ MoM = \frac{MoM}{\left(A + \frac{B}{Weight(kg)}\right)}$	Linear reciprocal [26]

Ultrasound gestation, BPD, CRL , AC [b]

Equation Type	One of the following equations can be chosen
Linear	$GA(days) = A + B \times x(mm)$
Quadratic	$GA(days) = A + B \times x(mm) + C \times x(mm)^2$
Cubic	$GA(days) = A + B \times x(mm) + C \times x(mm)^2 + D \times x(mm)^3$

Ultrasound gestation, Head Circumference (measured) [b]

The following equation can be selected for gestational age when head circumference is directly measured: [63]

$$Gestational\ age(days) = 7 \times e^{(0.010451\mathrm{HC} - 0.000029919\mathrm{HC}^2 + 0.43156 \times 10^{-7}\mathrm{HC}^3 + 1.854)}$$

where HC = head circumference measured in mm.

Ultrasound gestation, Head Circumference (derived) [b]

The following equation can be selected for gestational age when head circumference is derived from measurements of biparietal diameter and occipital-frontal diameter.[63]

$$Gestational\ age(days) = 7 \times e^{(0.010611\ \mathrm{HC} - 0.000030321\mathrm{HC}^2 + 0.43498 \times 10^{-7}\mathrm{HC}^3 + 1.848)}$$

where HC = head circumference measured in mm.

Ultrasound gestation, FASP [b]

The following equation, recommended by the UK Fetal Anomaly Screening Program (FASP) [72] , can be selected:

$$GA(days) = 8.052 \times (1.037 \times CRL(mm))^{½} + 23.73$$

a) For maternal serum markers only, separate median equations may be provided for:

Non-scan GA
Scan GA
Best GA

} Separately for overall population and up to 5 specified ethnic groups

The ethnic group specific medians are needed only if the **Ethnic group** prompt is included in the MS screen design. Separate medians for non-scan and scan GA are needed only if the corresponding median equation policy is to use separate equations *(see Section 3.1.8)*

b) Separate equations are available for each of the nine ultrasound machines selected by the **Machine** prompt

c) Separate equations relating median NT to CRL can be provided for individual sonographers.

d) This equation can also be expressed:

$$Expected\ inhibin\ median = A \times 1.000884123^{GA} \times 1.000532269^{(GA-120)^2} \times 0.999990723^{(GA-120)^3}$$

Where GA is the gestational age in days

Appendix E Message addition categories

Message addition can be used to add locally defined comments to MS or AF reports automatically. Different messages can be printed, depending on the type of report and the test results. The table below lists the different categories of message, and the circumstances in which they will appear on the report, if enabled.

Locally defined comments are preceded by the **Message addition system title**. The **Header message** and **Footer message** are used for messages that you wish to appear on all reports.

Some of the messages require one or more cut-off values before they can be enabled. Cut-off values are indicated by *x* and *y* in the table.

MATERNAL SERUM

Single category messages
Message addition system title
Header message[1]
Footer message[1]
Missing weight
Missing diabetes
Missing ethnic group
Missing previous Down's
Missing previous NTD
Clinical gestation only
Twin pregnancy
Age at EDD ≥ *x* years (specify *x*)
Increased risk of trisomy 18
Test at 14 weeks
Weight >= *x* kg (specify *x*)
Increased risk of SLOS
LMP based gestational age

Multiple category messages	
Screen negative	First test
	Repeat test
Screen positive NTD	Raised AFP, first test with scan
	Raised AFP, first test without scan
	Raised AFP, repeat test
	Previous NTD
Screen positive Down's	Increased Down's risk, first test with scan
	Increased Down's risk, first test without scan
	Increased Down's risk, repeat test
	Previous Down's syndrome
MS-AFP ≥ *x* MoM (specify *x*)[2]	First test with scan
	First test without scan
	Repeat test

MS-AFP ≤ *x* MoM (specify *x*)[2]	First test with scan First test without scan Repeat test
MS-AFP ≥ *x* MoM and < *y* MoM (specify *x* and *y*)[2]	First test with scan First test without scan Repeat test

AMNIOTIC FLUID

Single category messages
Message addition system title
Header message[1]
Footer message[1]
Negative
Positive (raised AFP, AChE not done)
Positive (raised AFP, AChE band present)
Ambiguous (AFP raised, AChE band absent)
Ambiguous (AFP not raised, AChE band present)

1 These messages can be either off, always on, or only on if other messages appear
2 These messages are for singleton pregnancies only

Appendix F Controlling access using security levels

Security level	Can access
1	All data entry facilities What-if
2	All level 1 facilities All reporting facilities except Correct/Update reports All statistics facilities Doctor and address codes
3	All level 1 and 2 facilities Correct/Update reports
4	All level 1, 2 and 3 facilities Access to all system menu options except: (i) add coefficients (ii) add parameters (iii) database check (iv) modify user list
5	All level 1, 2, 3 and 4 facilities Add coefficients Add parameters
6	All level 1, 2, 3, 4 and 5 facilities Database check Modify user list

Appendix G Import, Export, Data transfer and Analyze-it formats

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
Record number	Database record number	Integer	✔	✔	✘	✘	-	Derived	
Surname*	Patient's surname	Text (50)	✔	✔	✔	✔	A15	Entered	
Forename(s)*	Patient's forename	Text (50)	✔	✔	✔	✔	A15	Entered	
ID code*	Patient identification code	Text (50)	✔	✔	✔	✔	A14	Entered	Mandatory import field
Address 1*	Patient's address	Text (50)	✔	✔	✔	✔	A15	Entered	
Address 2*	Patient's address	Text (50)	✔	✔	✔	✔	A15	Entered	
Address 3*	Patient's address	Text (50)	✔	✔	✔	✔	A15	Entered	
Postcode*	Patient's post code	Text (10)	✔	✔	✔	✔	A10	Entered	
Phone number*	Patient's phone number	Text (50)	✔	✔	✔	✔	A10	Entered	
Doctor*	Doctor's name or doctor code	Text (50)	✔	✔	✔	✔	A15	Entered	Doctor's name or code (up to eight letters or numbers) identifying the doctor for this report (For import and export see note 12)
Report address*	Address code	Text (8)	✔	✔	✔	✔	A8	Entered	Code (up to eight letters or numbers) identifying the address for this report (For import and export see note 12)
Date of birth*	Patient's date of birth	Date	✔	✔	✔	✔	3I2	Entered	Mandatory import field
Age at EDD*	Age at expected date of delivery in	Integer	✔	✔	✔	✔	I2	Entered	Whole Years 12 years < age < 55 years

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
	data entry screen								
LMP*	Date of last menstrual period	Date	✔	✔	✔	✔	3I2	Entered	
EDD from LMP*	Expected date of delivery (from LMP)	Date	✔	✔	✔	✔	3I2	Entered	
Certain*	LMP or EDD from LMP date certainty	Integer	✔	✔	✔	✔	I1	Entered	1 = LMP or EDD date certain 2 = LMP or EDD date doubtful
GA by dates*	GA from LMP	Text (4)	✔	✔	✔	✔	I2,1X,I1	Entered	Weeks+days (eg 17+4)
GA by dates: On*	Date on which GA from LMP estimated	Date	✔	✔	✔	✔	3I2	Entered	
EDD from scan*	Expected date of delivery (from scan)	Date	✔	✔	✔	✔	3I2	Entered	
GA by scan*	GA from scan	Text (4)	✔	✔	✔	✔	I2,1X,I1	Entered	Weeks+days (eg 17+4)
GA by scan: On*	Date on which GA from scan estimated	Date	✔	✔	✔	✔	3I2	Entered	
GA by scan: Number fetuses*	Number of fetuses for GA by scan	Integer	✔	✔	✔	✔	I1	Entered	
GA by scan: Scan measure*	Type of ultrasound measurement for GA by scan	Integer	✔	✔	✔	✔	I1	Entered	1 = BPD in singleton fetus 2 = one BPD in twins 3 = both BPDs in twins 4 = other

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
									5 = not known
Date of scan*	Date of ultrasound scan	Date	✔	✔	✔	✔	3I2	Entered	
Date of scan: Machine*	Ultrasound machine number	Integer	✔	✔	✔	✔	I1	Entered	
Date of scan: Number fetuses*	Number of fetuses from ultrasound scan	Integer	✔	✔	✔	✔	I1	Entered	
Date of scan: Type of measure*	Type of ultrasound measurement	Integer	✔	✔	✔	✔	I1	Entered	1 = BPD 2 = CRL 3 = AC 4 = HC 10 mm < BPD < 110 mm 5 mm < CRL < 100 mm 30 mm < AC < 400 mm 80 mm < HC < 320 mm
Date of scan: Measurement (1)*	First fetus measurement	Text (5)	✔	✔	✔	✔	I3	Entered	mm
Date of scan: Measurement (2)*	Second fetus measurement	Text (5)	✔	✔	✔	✔	I3	Entered	mm
Type of measure*	Type of extra ultrasound measurement	Integer	✔	✔	✔	✔	I1	Entered	1 = BPD 2 = CRL 3 = AC

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
Type of measure: Measurement (1)*	First extra fetus measurement	Text (5)	✔	✔	✔	✔	I3	Entered	mm
Type of measure: Measurement (2)*	Second extra fetus measurement	Text (5)	✔	✔	✔	✔	I3	Entered	mm
Femur length(1)*	First fetus femur length	Integer	✔	✔	✔	✔	I3	Entered	mm
Femur length(2)*	Second fetus femur lengh	Integer	✔	✔	✔	✔	I3	Entered	mm
GA by clinical*	GA by clinical measurement	Integer	✔	✔	✔	✔	I2	Entered	days
GA by clinical: On*	Date GA by clinical measurement estimated	Date	✔	✔	✔	✔	3I2	Entered	
Date OC stopped*	Date oral contraception stopped	Date	✔	✔	✔	✔	3I2	Entered	
First or repeat*	No longer used		✔	✔	✔	✔	I1	Entered	
Weight*	Weight	Text (6)	✔	✔	✔	✔	F5.0	Entered	kgs or lbs 30 kg < weight < 200 kg 65 lbs < weight <440 lbs
Date weighed*	Date weighed	Date	✔	✔	✔	✔	3I2	Entered	
Previous Down's*	Type of previous pregnancy (if any)	Integer	✔	✔	✔	✔	I1	Entered	0 = none 1 = non-inherited

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
	affected with Down's syndrome								2 = inherited translocation 3 = type unknown
Previous NTD*	Number of previous pregnancies (if any) affected with open NTD.	Integer	✔	✔	✔	✔	I1	Entered	0 = none 1 = one 2 = two or more
Diabetes*	Diabetic status	Integer	✔	✔	✔	✔	I1	Entered	0 = none 1 = insulin-dependent diabetes mellitus
Ethnic group*	Ethnic group	Integer	✔	✔	✔	✔	I1	Entered	1 = black 2 = non-black 3 = not known 4 = group 4 5 = group 5 6 = group 6
Date of sample*	Date of (first) sample	Date	✔	✔	✔	✔	3I2	Entered	Mandatory import field
Previous amnio*	Date of last amniocentesis performed or attempted in this pregnancy.	Date	✔	✔	✔	✔	I1	Entered	
Date received*	Date sample received	Date	✔	✔	✔	✔	3I2	Entered	
Time received*	Time sample	Time	✔	✔	✔	✔	2I2	Entered	

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
	received								
Lab number*	Laboratory number (sample reference number)	Text (15)	✔	✔	✔	✔	A8	Entered	
Spare (1)*	Spare field 1	Text (100)	✔	✔	✔	✔	A15	Entered	
Spare (2)*	Spare field 2	Text (100)	✔	✔	✔	✔	A7	Entered	
Spare (3)*	Spare field 3	Text (100)	✔	✔	✔	✔	A7	Entered	
Spare (4)*	Spare field 4	Text (100)	✔	✔	✔	✔	A7	Entered	
Spare (5)*	Spare field 5	Text (100)	✔	✔	✔	✔	A7	Entered	
Spare (6)*	Spare field 6	Text (100)	✔	✔	✔	✔	A7	Entered	
Interpretation*	Specifies the type of interpretation required	Integer	✔	✔	✔	✔	I1	Entered	1 = Down's syndrome and NTD 2 = NTD only 3 = Down's syndrome only 4 = Down's syndrome, NTD and pre-eclampsia 5 = Down's syndrome and pre-eclampsia
Reports to*	Not used		✔	✔	✔	✔	A63	Entered	
Amniotic sacs*	The number of amniotic sacs in a twin pregnancy	Text (1)	✔	✔	✔	✔	I1	Entered	
Chorionic sacs*	The number of chorionic sacs in a	Text (1)	✔	✔	✔	✔	I1	Entered	

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
	twin pregnancy								
MS-AFP	MS-AFP level	Text (6)	✔	✔	✔	✔	A5	Entered	NT levels are formatted according to Note 11 For import, export and analyze-it the first character is "<" if the measurement is less than the number following the "<" symbol. For data transfer the "<" is removed and the corresponding level flag should be used to check if the level is less than the value given.
uE3	uE3 level	Text (6)	✔	✔	✔	✔	A5	Entered	
T-hCG	total hCG level	Text (7)	✔	✔	✔	✔	A6	Entered	
Marker 4	Marker 4 level	Text (7)	✔	✔	✔	✔	A6	Entered	
Marker 5	Marker 5 level	Text (7)	✔	✔	✔	✔	A6	Entered	
Marker 6	Marker 6 level	Text (7)	✔	✔	✔	✔	A6	Entered	
Marker 7	Marker 7 level	Text (7)	✔	✔	✔	✔	A6	Entered	
Marker 8	Marker 8 level	Text (7)	✔	✔	✔	✔	A6	Entered	
Marker 9	Marker 9 level	Text (7)	✔	✔	✔	✔	A6	Entered	
Marker 10	Marker 10 level	Text (7)	✔	✔	✔	✔	A6	Entered	
Marker 11	Marker 11 level	Text (7)	✔	✔	✔	✔	A6	Entered	
Marker 12	Marker 12 level	Text (7)	✔	✔	✔	✔	A6	Entered	
Date of 2nd sample*	Date of second sample for integrated test	Date	✔	✔	✔	✔	3I2	Entered	
Integrated screening*	Integrated screening	Integer	✔	✔	✔	✔	I1	Entered	0=No 1=Standard integrated (Combining the results of the first and second trimester markers) 2=Sequential testing (Only women who have a negative

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
									first trimester test proceed to the full Integrated test)
Sonographer*	Sonographer code	Text (8)	✔	✔	✔	✔	I8.8	Entered	Code (up to 8 letters or numbers) identifying the sonographer who made the nuchal translucency (NT) measurement. (For import and export See note 12) Mandatory import field for the Integrated test
IVF pregnancy*	IVF pregnancy	Integer	✔	✔	✔	✔	I1	Entered	0=No 1=Yes
Weight units*	Not used – see Weight flag		✔	✔	✔	✔	I1	Entered	
Date 2nd sample recd*	Date second sample received for integrated test	Date	✔	✔	✔	✔	3I2	Entered	
Time 2nd sample recd*	Time second sample received for integrated test	Time	✔	✔	✔	✔	2I2	Entered	
Smoker*	Smoker	Integer	✔	✔	✔	✔	I1	Entered	0=No 1=Yes
Donor date of birth*	The donor's date of birth in an IVF pregnancy in which the egg is donated.	Date	✔	✔	✔	✔	3I2	Entered	
Donor age at EDD*	The donor's age at the expected date	Integer	✔	✔	✔	✔	I2	Entered	Years 12 years < age < 55 years

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
	of delivery in an IVF pregnancy in which the egg is donated, and the donor's date of birth is not known.								
Date embryo transfer*	In an IVF pregnancy, the date of embryo transfer	Date	✔	✔	✔	✔	3I2	Entered	
Nasal bone (fetus 1)*	Nasal bone status (first fetus)	Integer	✔	✔	✔	✔	I1	Entered	0 = absent 1 = present 2= not reported
Nasal bone (fetus 2)*	Nasal bone status (second fetus)	Integer	✔	✔	✔	✔	I1	Entered	0 = absent 1 = present 2= not reported
Age at prev. preg.*	The age at which a previous pregnancy was affected with Down's syndrome	Integer	✔	✔	✔	✔	I2	Entered	Years
Date egg collection*	In an IVF pregnancy using a frozen embryo, the date of egg collection	Date	✔	✔	✔	✔	3I2	Entered	

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
Prev. Pre-eclampsia*	Previous pre-eclampsia	Integer	✔	✔	✔	✔	I1	Entered	0 = No 1 = Yes
Ductus venosus blood flow*	Ductus venosus blood flow	Integer	✔	✔	✔	✔	I1	Entered	0 = Reverse or absent 1 = Forward 2 = Not reported
Patient flag	Not used		✔	✔	✔	✘	-	Derived	
Date entered	Date patient data first entered	Date	✔	✔	✔	✘	3I2	Derived	
Date reported	Date report made	Date	✔	✔	✔	✘	3I2	Derived	
Repeat flag	Shows if report is a first or repeat test	Text (1)	✔	✔	✘	✘	--	Derived	1 - initial test or broken match R - repeat test ? - means that pointers have changed since original report
Correct/update flag (1)	Report is an update (modification of dating) or correction (any other change)	Text (1)	✔	✔	✘	✘	-	Derived	C - correction of a non-updated report S - scan update s - correction of scan update
Correct/update flag (2)	Report has been corrected or updated	Text (1)	✔	✔	✘	✘	-	Derived	Copy of Correct/update flag (1) in the later test
Pointer forward	Report has been corrected, updated or is the initial test of a repeat test	Integer	✔	✔	✘	✘	-	Derived	Record number of corrected report or repeat test preceded by M if report is MS-AF or A if AF-AFP

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
Pointer forward type	Type of corrected report	Integer	✔	✔	✘	✘	-	Derived	0 - MS 1 - AF 2 - NTD only
Pointer back	Report is a correction, update or a repeat test	Integer	✔	✔	✘	✘	-	Derived	Record number of previous report preceded by M if report is MS-AF or A if AF-AFP
Pointer back type	Type of previous report	Integer	✔	✔	✘	✘	-	Derived	0 - MS 1 - AF
Delete status flag	Delete flag. If set record is not included in statistical tabulations	Text(1)	✔	✔	✘	✘	-	Derived	D - record deleted
Update flag	Not used		✔	✔	✘	✘	-	Derived	
Version flag	Not used		✔	✔	✘	✘	-	Derived	
Age at EDD (decimal)	Age at expected date of delivery (calculated with decimal fraction)	Single	✔	✔	✔	✘	I2	Derived	Years and decimal fraction
AFP MoM			✔	✔	✔	✘	A5	Derived	Serum marker MoMs are corrected for weight and ethnicity but not twins, IVF, smoking or diabetic status.
uE3 MoM			✔	✔	✔	✘	A5	Derived	

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
hCG MoM			✔	✔	✔	✘	A5	Derived	For Export and Analyze-it, if the MoM is negative this indicates that the MoM is less than the absolute value of the number shown. For data transfer, the corresponding MoM flag should be checked to see if the marker MoM is less than the value given. NT MoM values in twins are formatted according to Note 15
Marker 4 MoM			✔	✔	✔	✘	A5	Derived	
Marker 5 MoM			✔	✔	✔	✘	A5	Derived	
Marker 6 MoM			✔	✔	✔	✘	A5	Derived	
Marker 7 MoM			✔	✔	✔	✘	A5	Derived	
Marker 8 MoM			✔	✔	✔	✘	A5	Derived	
Marker 9 MoM			✔	✔	✔	✘	A5	Derived	
Marker 10 MoM			✔	✔	✔	✘	A5	Derived	
Marker 11 MoM			✔	✔	✔	✘	A5	Derived	
Marker 12 MoM			✔	✔	✔	✘	A5	Derived	
Scan GA at 1st sample	GA by scan for (first) sample	Integer	✔	✔	✔	✘	I3	Derived	Days
Dates GA at 1st sample	GA by dates for (first) sample	Integer	✔	✔	✔	✘	I3	Derived	Days
Clinical GA at 1st sample	Clinical GA for first sample	Integer	✔	✔	✔	✘	I3	Derived	Days
Scan GA at 2nd sample	GA by scan for second sample of Integrated test	Integer	✔	✔	✔	✘	I3	Derived	Days
Dates GA at 2nd sample	GA by dates for second sample of	Integer	✔	✔	✔	✘	I3	Derived	Days

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
	Integrated test								
Clinical GA at 2nd sample	Clinical GA for second sample of Integrated test	Integer	✔	✔	✔	✘	I3	Derived	Days
Positivity	Positivity flag	Text (1)	✔	✔	✔	✘	A1	Derived	+ : Screening result positive - : Screening result negative T : Increased risk of trisomy 18 (negative for Down's) S: Increased risk of SLOS (negative for Down's) 3: Increased risk of Trisomy 13 (negative for Down's) U : uninterpretable
Down's prior risk	Prior Downs risk (rounded)	Long Integer	✔	✔	✔	✘	A5	Derived	
Down's prior (unrounded)	Prior Downs risk (unrounded)	Long Integer	✔	✔	✘	✘	-	Derived	
Down's risk flag	Shows if Down's risk has been trimmed or capped	Text (1)	✔	✔	✘	✘	-	Derived	< : risk has been trimmed > : risk has been capped Note: if the data exported includes a twin pregnancy an additional field Down's risk flag (twin 2) is exported. This can be ignored.
Down's risk LHS	Down's syndrome risk left hand side	Long Integer	✔	✔	✘	✘	-	Derived	*In a twin pregnancy, this is a pseudo risk and should be indicated as such.*
Down's risk RHS	Down's syndrome risk right hand side	Long Integer	✔	✔	✘	✘	-	Derived	

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
	(rounded)								
Down's risk LHS (unrounded)	Down's syndrome risk left hand side	Long Integer	✔	✔	✖	✖	-	Derived	
Down's risk RHS (unrounded)	Down's syndrome risk right hand side (unrounded)	Long Integer	✔	✔	✖	✖	-	Derived	
Down's risk (post)	Down's syndrome posterior risk (See note 14)		✖	✖	✔	✖	A12	Derived	
NTD prior risk	NTD prior risk (rounded)	Long Integer	✔	✔	✔	✖	A5	Derived	
NTD prior (unrounded)	NTD prior risk (unrounded)	Long Integer	✔	✔	✖	✖	-	Derived	
NTD risk flag	Shows if risk has been trimmed or capped	Text (1)	✔	✔	✖	✖	-	Derived	< : risk has been trimmed > : risk has been capped
NTD risk LHS	NTD risk right hand side (rounded)	Long Integer	✔	✔	✖	✖	-	Derived	
NTD risk RHS	NTD risk right hand side (unrounded)	Long Integer	✔	✔	✖	✖	-	Derived	
NTD risk LHS (unrounded)	NTD risk left hand side	Long Integer	✔	✔	✖	✖	-	Derived	
NTD risk RHS (unrounded)	NTD risk right hand side (unrounded)	Long Integer	✔	✔	✖	✖	-	Derived	

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
NTD risk (post)	NTD posterior risk (See note 14)		✗	✗	✓	✗	A12	Derived	
Trisomy 18 prior risk	Trisomy 18 prior risk (rounded)	Long Integer	✓	✓	✓	✗	A5	Derived	
Trisomy 18 prior (unrounded)	Trisomy 18 prior risk (unrounded)	Long Integer	✓	✓	✗	✗	-	Derived	
Trisomy 18 risk flag	Shows if risk has been trimmed or capped	Text (1)	✓	✓	✗	✗	-	Derived	< : risk has been trimmed > : risk has been capped
Trisomy 18 risk LHS	Trisomy 18 risk left hand side	Long Integer	✓	✓	✗	✗	-	Derived	*The trisomy 18 risk can only be reported when it is above the screening cut-off and should not be reported in twin or diabetic pregnancies.*
Trisomy 18 risk RHS	Trisomy 18 risk right hand side (rounded)	Long Integer	✓	✓	✗	✗	-	Derived	
Trisomy 18 risk LHS (unrounded)	Trisomy 18 risk left hand side	Long Integer	✓	✓	✗	✗	-	Derived	
Trisomy 18 risk RHS (unrounded)	Trisomy 18 risk right hand side (unrounded)	Long Integer	✓	✓	✗	✗	-	Derived	
Trisomy 18 risk (post)	Trisomy 18 posterior risk (See note 14)		✗	✗	✓	✗	A12	Derived	
SLOS prior risk	SLOS prior risk (rounded)	Long Integer	✓	✓	✓	✗	A5	Derived	

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
SLOS prior (unrounded)	SLOS prior risk (unrounded)	Long Integer	✔	✔	✘	✘	-	Derived	
SLOS risk flag	Shows if risk has been trimmed or capped	Text (1)	✔	✔	✘	✘	-	Derived	< : risk has been trimmed > : risk has been capped
SLOS risk LHS	SLOS risk (rounded)	Long Integer	✔	✔	✘	✘	-	Derived	*The SLOS risk can only be reported when it is above the screening cut-off and should not be reported in twin or diabetic pregnancies.*
SLOS risk RHS	SLOS risk (unrounded)	Long Integer	✔	✔	✘	✘	-	Derived	
SLOS risk LHS (unrounded)	SLOS risk left hand side	Long Integer	✔	✔	✘	✘	-	Derived	
SLOS risk RHS (unrounded)	SLOS risk right hand side (unrounded)	Long Integer	✔	✔	✘	✘	-	Derived	
SLOS risk (post)	SLOS posterior risk (See note 14)		✘	✘	✔	✘	A12	Derived	
Pre-Eclampsia prior risk	Pre-eclampsia prior risk (rounded)	Long Integer	✔	✔	✔	✘	A5	Derived	
Pre-Eclampsia prior risk (unrounded)	Pre-eclampsia prior risk (unrounded)	Long Integer	✔	✔	✘	✘	-	Derived	
Pre-Eclampsia risk flag	Shows if risk has been trimmed or capped	Text (1)	✔	✔	✘	✘	-	Derived	< : risk has been trimmed > : risk has been capped
Pre-Eclampsia risk LHS	Pre-eclampsia risk	Long	✔	✔	✘	✘	-	Derived	

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
	left hand side	Integer							
Pre-Eclampsia risk RHS	Pre-eclampsia risk right hand side (rounded)	Long Integer	✔	✔	✖	✖	-	Derived	
Pre-Eclampsia risk LHS (unrounded)	Pre-eclampsia risk left hand side	Long Integer	✔	✔	✖	✖	-	Derived	
Pre-Eclampsia risk RHS (unrounded)	Pre-eclampsia risk right hand side (unrounded)	Long Integer	✔	✔	✖	✖	-	Derived	
Pre-Eclampsia risk (post)	Pre-eclampsia posterior risk (See note 14)		✖	✖	✔	✖	A12	Derived	
Trisomy 13 prior risk	Trisomy 13 prior risk (rounded)	Long Integer	✔	✔	✔	✖	A5	Derived	
Trisomy 13 prior risk (unrounded)	Trisomy 13 prior risk (unrounded)	Long Integer	✔	✔	✖	✖	-	Derived	
Trisomy 13 risk flag	Shows if risk has been trimmed or capped	Text (1)	✔	✔	✖	✖	-	Derived	< : risk has been trimmed > : risk has been capped
Trisomy 13 risk LHS	Trisomy 13 risk left hand side	Long Integer	✔	✔	✖	✖	-	Derived	*The trisomy 13 risk can only be reported when it is above the screening cut-off and should not be reported in twin or diabetic pregnancies.*
Trisomy 13 risk RHS	Trisomy 13 risk right hand side (rounded)	Long Integer	✔	✔	✖	✖	-	Derived	

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
Trisomy 13 risk LHS (unrounded)	Trisomy 13 risk left hand side	Long Integer	✔	✔	✘	✘	-	Derived	
Trisomy 13 risk RHS (unrounded)	Trisomy 13 risk right hand side (unrounded)	Long Integer	✔	✔	✘	✘	-	Derived	
Trisomy 13 risk (post)	Trisomy 13 posterior risk (See note 14)		✘	✘	✔	✘	A12	Derived	
Trisomy 18 flag	Trisomy 18 flag	Text(1)	✔	✔	✔	✘	A1	Derived	+ : increased risk of trisomy 18 - : trisomy 18 risk below threshold
Trisomy 13 flag	Trisomy 13 flag	Text(1)	✔	✔	✔	✘	A1	Derived	+ : increased risk of trisomy 13 - : trisomy 13 risk below threshold
SLOS Flag	SLOS Flag	Text(1)	✔	✔	✔	✘	A1	Derived	+ : increased risk of SLOS - : SLOS risk below threshold
AFP MoM for NTD screening	AFP MoM for NTD screening	Single	✔	✔	✔	✘	A5	Derived	MoMs are corrected for weight and ethnicity but not twins, IVF, smoking or diabetic status.
Trimester flag	Shows which trimester this measurement was taken in	Text (1)	✔	✔	✘	✘	-	Derived	1 = first trimester 2 = second trimester 3 = integrated test
Weight Flag	Units in which the weight was entered	Integer	✔	✔	✘	✘	-	Entered	0 : kg 1 : lbs
User	Username of user who started data	Text(50)	✔	✔	✘	✘	-	Entered	Format is: <Username of user who started data entry>,<username of

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
	entry and username of user who made final report								user who made final report> For corrections, only the name of the user who made the correction is stored.
Comment	Text entered if a correction or update	Text (255)	✔	✔	✘	✘	-	Entered	
Time entered	Time patient data first entered	Time	✔	✔	✔	✘	-	Derived	
Doctor 2	Doctor code or name for second doctor to send report to	Text (50)	✔	✔	✘	✘	-	Entered	
Report address 2	Address code for second address to send report to	Text (8)	✔	✔	✘	✘	-	Entered	
Doctor 3	Doctor code or name for third doctor to send report to	Text (50)	✔	✔	✘	✘	-	Entered	
Report address 3	Address code for third address to send report to	Text (8)	✔	✔	✘	✘	-	Entered	
Language 1	Language code for report of first doctor	Integer	✔	✔	✘	✘	-	Entered	1- English, 2-German, 3-Italian, 4-French, 5-Greek, 6-Czech, 7-Spanish, 8-Portuguese, 9-Russian, 10-Turkish, 11-Slovak, 12-Vietnamese, 13-Romanian, 14-Chinese,
Language 2	Language code for	Integer	✔	✔	✘	✘	-	Entered	

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
	report of second doctor								15-Polish.
Language 3	Language code for report of third doctor	Integer	✔	✔	✘	✘	-	Entered	
Reason code	Reason for positive or un-interpretable result		✔	✔	✔	✘	A1	Derived	For positive and un-interpretable results only See note 16.
Integrated test flags	Not used		✘	✔	✘	✘	-	Derived	
Age at EDD (calculated)	Age at expected data of delivery (calculated)	Integer	✔	✔	✘	✘	-	Derived	Whole Years
Donor's age at EDD (calculated)	Donor's age at expected date of delivery	Integer	✔	✔	✔	✘	-	Derived	Completed years
EDD (calculated)	Expected date of delivery (calculated)	Date	✔	✔	✔	✘	-	Derived	
RFP Pointer	If there is a value, then MoM values were adjusted using measurements taken in a previous pregnancy	Long Integer	✔	✔	✘	✘	-	Derived	Record number of matched pregnancy

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
AFP Assay Date	Date on which the marker was measured. This is used to determine the chronogically correct regression equation coefficients to use	Date	✔	✔	✔	✔	3I2	Entered	
uE3 Assay Date		Date	✔	✔	✔	✔	3I2	Entered	
hCG Assay Date		Date	✔	✔	✔	✔	3I2	Entered	
Marker 4 Assay Date		Date	✔	✔	✔	✔	3I2	Entered	
Marker 5 Assay Date		Date	✔	✔	✔	✔	3I2	Entered	
Marker 6 Assay Date		Date	✔	✔	✔	✔	3I2	Entered	
Marker 7 Assay Date		Date	✔	✔	✔	✔	3I2	Entered	
Marker 8 Assay Date		Date	✔	✔	✔	✔	3I2	Entered	
Marker 9 Assay Date		Date	✔	✔	✔	✔	3I2	Entered	
Marker 10 Assay Date		Date	✔	✔	✔	✔	3I2	Entered	
Marker 11 Assay Date		Date	✔	✔	✔	✔	3I2	Entered	
Marker 12 Assay Date		Date	✔	✔	✔	✔	3I2	Entered	
AFP level flag	Specifies if the marker measurement was below the entered value	Text(1)	✘	✔	✘	✘	-	Derived	Contains '<' if measurement was below the entered marker level.
uE3 level flag		Text(1)	✘	✔	✘	✘	-	Derived	
hCG level flag		Text(1)	✘	✔	✘	✘	-	Derived	
Marker 4 level flag		Text(1)	✘	✔	✘	✘	-	Derived	
Marker 5 level flag		Text(1)	✘	✔	✘	✘	-	Derived	
Marker 6 level flag		Text(1)	✘	✔	✘	✘	-	Derived	

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
Marker 7 level flag		Text(1)	✗	✓	✗	✗	-	Derived	
Marker 8 level flag		Text(1)	✗	✓	✗	✗	-	Derived	
Marker 9 level flag		Text(1)	✗	✓	✗	✗	-	Derived	
Marker 10 level flag		Text(1)	✗	✓	✗	✗	-	Derived	
Marker 11 level flag		Text(1)	✗	✓	✗	✗	-	Derived	
Marker 12 level flag		Text(1)	✗	✓	✗	✗	-	Derived	
AFP MoM flag	Specifies if the marker marker MoM was below the value shown	Text(1)	✗	✓	✗	✗	-	Derived	Contains '<' if the MoM value was below the value shown
uE3 MoM flag		Text(1)	✗	✓	✗	✗	-	Derived	
hCG MoM flag		Text(1)	✗	✓	✗	✗	-	Derived	
Marker 4 MoM flag		Text(1)	✗	✓	✗	✗	-	Derived	
Marker 5 MoM flag		Text(1)	✗	✓	✗	✗	-	Derived	
Marker 6 MoM flag		Text(1)	✗	✓	✗	✗	-	Derived	
Marker 7 MoM flag		Text(1)	✗	✓	✗	✗	-	Derived	
Marker 8 MoM flag		Text(1)	✗	✓	✗	✗	-	Derived	
Marker 9 MoM flag		Text(1)	✗	✓	✗	✗	-	Derived	
Marker 10 MoM flag		Text(1)	✗	✓	✗	✗	-	Derived	
Marker 11 MoM flag		Text(1)	✗	✓	✗	✗	-	Derived	
Marker 12 MoM flag		Text(1)	✗	✓	✗	✗	-	Derived	

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
NTD AFP MoM flag		Text(1)	✗	✔	✗	✗	-	Derived	
AFP MoM adjusted	MoM including adjustments	Single	✗	✔	✗	✗	-	Derived	Adjusted serum marker MoM including corrections for weight , ethnicity and (if appropriate) twins, IVF, smoking or diabetic status.
uE3 MoM adjusted		Single	✗	✔	✗	✗	-	Derived	
hCG MoM adjusted		Single	✗	✔	✗	✗	-	Derived	
Marker 4 MoM adjusted		Single	✗	✔	✗	✗	-	Derived	
Marker 5 MoM adjusted		Single	✗	✔	✗	✗	-	Derived	
Marker 6 MoM adjusted		Single	✗	✔	✗	✗	-	Derived	
Marker 7 MoM adjusted		Single	✗	✔	✗	✗	-	Derived	
Marker 8 MoM adjusted		Single	✗	✔	✗	✗	-	Derived	
Marker 9 MoM adjusted		Single	✗	✔	✗	✗	-	Derived	
Marker 10 MoM adjusted		Single	✗	✔	✗	✗	-	Derived	
Marker 11 MoM adjusted		Single	✗	✔	✗	✗	-	Derived	
Marker 12 MoM adjusted		Single	✗	✔	✗	✗	-	Derived	
Down's risk (superseded)	Down's syndrome risk (rounded). Field superseded - see comment.		✗	✔	✗	✗	-	Derived	Deprecated field: This field exports risks no greater than 1/2
NTD risk (superseded)	NTD risk (rounded). Field superseded - see comment.		✗	✔	✗	✗	-	Derived	

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
Trisomy 18 risk (superseded)	Trisomy 18 risk (rounded). Field superseded - see comment.		✗	✓	✗	✗	-	Derived	
SLOS risk (superseded)	SLOS risk (rounded). Field superseded - see comment.		✗	✓	✗	✗	-	Derived	
Pre-Eclampsia risk (superseded)	Pre-eclampsia risk (rounded). Field superseded - see comment.		✗	✓	✗	✗	-	Derived	
Trisomy 13 risk (superseded)	Trisomy 13 risk (rounded). Field superseded - see comment.		✗	✓	✗	✗	-	Derived	
Unrounded Down's risk (superseded)	Down's syndrome risk (unrounded). Field superseded - see comment.		✗	✓	✗	✗	-	Derived	
Unrounded NTD risk (superseded)	NTD risk (unrounded). Field superseded - see comment.		✗	✓	✗	✗	-	Derived	

Maternal Serum									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
Unrounded Trisomy 18 risk (superseded)	Trisomy 18 risk (unrounded). Field superseded - see comment.		✗	✓	✗	✗	-	Derived	
Unrounded SLOS risk (superseded)	SLOS risk (unrounded). Field superseded - see comment.		✗	✓	✗	✗	-	Derived	
Unrounded Pre-Eclampsia risk (superseded)	Pre-eclampsia risk (unrounded). Field superseded - see comment.		✗	✓	✗	✗	-	Derived	
Unrounded Trisomy 13 risk (superseded)	Trisomy 13 risk (unrounded). Field superseded - see comment.		✗	✓	✗	✗	-	Derived	

Amniotic Fluid									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
Record number	Database record number	Integer	✔	✔	✘	✘		Derived	
Surname*	Patient's surname	Text (50)	✔	✔	✔	✔	A15	Entered	
Forename(s)*	Patient's forename	Text (50)	✔	✔	✔	✔	A15	Entered	
ID code*	Patient identification code	Text (50)	✔	✔	✔	✔	A14	Entered	
Address 1*	Patient's address	Text (50)	✔	✔	✔	✔	A15	Entered	
Address 2*	Patient's address	Text (50)	✔	✔	✔	✔	A15	Entered	
Address 3*	Patient's address	Text (50)	✔	✔	✔	✔	A15	Entered	
Postcode*	Patient's post code	Text (10)	✔	✔	✔	✔	A10	Entered	
Phone number*	Patient's phone number	Text (50)	✔	✔	✔	✔	A10	Entered	
Doctor*	Doctor's name or doctor code	Text (50)	✔	✔	✔	✔	A15	Entered	Doctor's name or code (up to eight letters or numbers) identifying the doctor for this report (For import and export see note 12)
Report address*	Address code	Text (8)	✔	✔	✔	✔	A8	Entered	Code (up to eight letters or numbers) identifying the address for this report (For import and export see note 12)
Date of birth*	Patient's date of birth	Date	✔	✔	✔	✔	3I2	Entered	
Age at EDD*	Age at expected date of delivery in data entry screen	Integer	✔	✔	✔	✔	I2	Entered	Whole Years 12 years < age < 55 years

Amniotic Fluid									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
LMP*	Date of last menstrual period	Date	✔	✔	✔	✔	3I2	Entered	
EDD from LMP*	Expected date of delivery (from LMP)	Date	✔	✔	✔	✔	3I2	Entered	
Certain*	LMP date certainty	Integer	✔	✔	✔	✔	I1	Entered	1 = LMP date certain 2 = LMP date doubtful
GA by dates*	GA from LMP	Text (4)	✔	✔	✔	✔	I2,1X,I1	Entered	Weeks+days (eg 17+4)
GA by dates: On*	Date on which GA from LMP estimated	Date	✔	✔	✔	✔	3I2	Entered	
EDD from scan*	Expected date of delivery (from scan)	Date	✔	✔	✔	✔	3I2	Entered	
GA by scan*	GA from scan	Text (4)	✔	✔	✔	✔	I2,1X,I1	Entered	Weeks+days (eg 17+4)
GA by scan: On*	Date on which GA from scan estimated	Date	✔	✔	✔	✔	3I2	Entered	
GA by scan: Number fetuses*	Number of fetuses for GA by scan	Integer	✔	✔	✔	✔	I1	Entered	
GA by scan: Scan measure*	Type of ultrasound measurement for GA by scan	Integer	✔	✔	✔	✔	I1	Entered	1 = BPD in singleton fetus 2 = one BPD in twins 3 = both BPDs in twins 4 = other 5 = not known

Amniotic Fluid									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
Date of scan*	Date of ultrasound scan	Date	✔	✔	✔	✔	3I2	Entered	1 = BPD 2 = CRL 3 = AC 4 = HC 10 mm < BPD < 110 mm 5 mm < CRL < 100 mm 30 mm < AC < 400 mm 80 mm < HC < 320 mm
Date of scan: Machine*	Ultrasound machine number	Integer	✔	✔	✔	✔	I1	Entered	mm
Date of scan: Number fetuses*	Number of fetuses from ultrasound scan	Integer	✔	✔	✔	✔	I1	Entered	
Date of scan: Type of measure*	Type of ultrasound measurement	Integer	✔	✔	✔	✔	I1	Entered	1 = BPD 2 = CRL 3 = AC
Date of scan: Measurement (1)*	First fetus measurement	Text (5)	✔	✔	✔	✔	I3	Entered	mm
Date of scan: Measurement (2)*	Second fetus measurement	Text (5)	✔	✔	✔	✔	I3	Entered	mm
Femur length(1)*	First fetus femur length	Integer	✔	✔	✔	✔	I3	Entered	mm
Femur length(2)*	Second fetus femur lengh	Integer	✔	✔	✔	✔	I3	Entered	mm

Amniotic Fluid									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
GA by clinical*	GA by clinical measurement	Integer	✔	✔	✔	✔	I2	Entered	days
GA by clinical: On*	Date GA by clinical measurement estimated	Date	✔	✔	✔	✔	3I2	Entered	
Date OC stopped*	Date oral contraception stopped	Date	✔	✔	✔	✔	2I2	Entered	
First or repeat*	No longer used		✔	✔	✔	✔	I1	Entered	
Ethnic group*	Ethnic group	Integer	✔	✔	✔	✔	I1	Entered	1 = black 2 = non-black 3 = not known 4 = group 4 5 = group 5 6 = group 6
Diabetes*	Diabetic status	Integer	✔	✔	✔	✔	I1	Entered	0 = none 1 = insulin-dependent diabetes mellitus
Previous NTD*	Number of previous pregnancies (if any) affected with open NTD.	Integer	✔	✔	✔	✔	I1	Entered	0 = none 1 = one 2 = two or more
Amnio reason*	Reason for amniocentesis	Integer	✔	✔	✔	✔	I1	Entered	1 = raised MS-AFP 2 = suspicion of NTD on ultrasound 3 = previous suspicious AF-AFP/AChE

Amniotic Fluid									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
									4 = family history of NTD 5 = increased risk of Down's syndrome 6 = unrelated to NTD or Down's risk 7 = advanced maternal age 8 = abnormal ultrasound finding 9 = increased risk of trisomy 18
Date of sample*	Date of sample	Date	✔	✔	✔	✔	3I2	Entered	
AF appearance*	Sample appearance	Integer	✔	✔	✔	✔	I1	Entered	1 = clear 2 = cloudy 3 = frankly bloodstained 4 = significantly discoloured
AF-AFP*	AF-AFP marker level	Text(6)	✔	✔	✔	✔	A5	Entered	
AChE NTD band*	AChE NTD band	Integer	✔	✔	✔	✔	I1	Entered	1 = faint 2 = strong 3 = absent 4 = pending
PChE bands*	PChE band	Integer	✔	✔	✔	✔	I1	Entered	1 = single 2 = multiple 3 = absent 4 = pending
Fetal cells (%)*	Result of AF-Kleihauer test	Integer	✔	✔	✔	✔	I3	Entered	Percentage
RBC(million/ml)*	Red blood cell	Integer	✔	✔	✔	✔	I3	Entered	million/ml

Amniotic Fluid									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
Date received*	Date sample received	Date	✔	✔	✔	✔	3I2	Entered	
Time received*	Time sample received	Time	✔	✔	✔	✔	2I2	Entered	
Lab number*	Laboratory number (sample reference number)	Text (15)	✔	✔	✔	✔	A8	Entered	
Spare (1)*	Spare field 1	Text (100)	✔	✔	✔	✔	A15	Entered	
Spare (2)*	Spare field 2	Text (100))	✔	✔	✔	✔	A7	Entered	
Spare (3)*	Spare field 3	Text (100)	✔	✔	✔	✔	A7	Entered	
Spare (4)*	Spare field 4	Text (100)	✔	✔	✔	✔	A7	Entered	
Spare (5)*	Spare field 5	Text (100)	✔	✔	✔	✔	A7	Entered	
Spare (6)*	Spare field 6	Text (100)	✔	✔	✔	✔	A7	Entered	
Reports to	Not used		✔	✔	✔	✔	A63	Entered	
Patient flag	Not used		✔	✔	✔	✘		Derived	
Date entered	Date patient data first entered	Date	✘	✔	✔	✘	3I2	Derived	
Date reported	Date report made	Date	✔	✔	✔	✘	3I2	Derived	
Repeat flag	Shows if report is a first or repeat test	Text (1)	✔	✔	✘	✘		Derived	1 - initial test or broken match R - repeat test ? - means that pointers have changed since original report

Amniotic Fluid									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
Correct/update flag (1)	Report is an update (modification of dating) or correction (any other change)	Text (1)	✔	✔	✖	✖		Derived	C - correction of a non-updated report S - scan update s - correction of scan update
Correct/update flag (2)	Report has been corrected or updated	Text (1)	✔	✔	✖	✖		Derived	Copy of Correct/update flag (1) in the later test
Pointer forward	Report has been corrected, updated or is the initial test of a repeat test	Integer	✔	✔	✖	✖		Derived	Record number of corrected report or repeat test preceded by M if report is MS-AF or A if AF-AFP
Pointer forward type	Type of corrected report	Integer	✔	✔	✖	✖		Derived	0 - MS 1 - AF 2 - NTD only
Pointer back	Report is a correction, update or a repeat test	Integer	✔	✔	✖	✖		Derived	Record number of previous report preceded by M if report is MS-AF or A if AF-AFP
Pointer back type	Type of previous report	Integer	✔	✔	✖	✖		Derived	0 - MS 1 - AF
Delete status flag	Delete flag. If set record is not included in statistical	Text(1)	✔	✔	✖	✖		Derived	D - record deleted

Amniotic Fluid									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
	tabulations								
Update flag	Not used		✔	✔	✘	✘		Derived	
Version flag	Not used		✔	✔	✘	✘		Derived	
AF-AFP MoM	AF-AFP MoM value	Single	✔	✔	✔	✘	A5	Derived	
Scan gestation (days)			✔	✔	✔	✘	I3	Derived	Days
Dates gestation (days)			✔	✔	✔	✘	I3	Derived	Days
Clinical gestation (days)			✔	✔	✔	✘	I3	Derived	Days
Positivity	AF-AFP Positivity flag		✔	✔	✔	✘	A1	Derived	+ : positive - : negative U : uninterpretable
User	Username of user who started data entry and username of user who made final report	Text(50)	✔	✔	✘	✘		Derived	Format is: <Username of user who started data entry>,<username of user who made final report> For corrections, only the name of the user who made the correction is stored.
Comment	Text entered if a correction or update	Text (255)	✔	✔	✘	✘		Derived	
Time entered	Time patient data first entered	Time	✔	✔	✔	✘		Derived	
Doctor 2	Doctor code or name for second doctor to send	Text (50)	✔	✔	✘	✘		Derived	

Amniotic Fluid									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
	report to								
Report address 2	Address code for second address to send report to	Text (8)	✔	✔	✘	✘		Derived	
Doctor 3	Doctor code or name for third doctor to send report to	Text (50)	✔	✔	✘	✘		Derived	
Report address 3	Address code for third address to send report to	Text (8)	✔	✔	✘	✘		Derived	
Language 1	Language code for report of first doctor	Integer	✔	✔	✘	✘		Derived	1- English, 2-German, 3-Italian, 4-French, 5-Greek, 6-Czech, 7-Spanish, 8-Portuguese, 9-Russian, 10-Turkish, 11-Slovak, 12-Vietnamese, 13-Romanian, 14-Chinese, 15-Polish.
Language 2	Language code for report of second doctor	Integer	✔	✔	✘	✘		Derived	
Language 3	Language code for report of third doctor	Integer	✔	✔	✘	✘		Derived	
Reason code	Reason for positive or un-interpretable result	Text	✔	✔	✔	✘	A1	Derived	For positive and un-interpretable results only See note 16
EDD (calculated)	Expected date of delivery (calculated)	Date	✔	✔	✔	✘	3I2	Derived	

Amniotic Fluid									
Field name	**Meaning**	**Type of field**	**Analyze-it**	**Data transfer**	**Export**	**Import**	**Fixed width format (for import and export)**	**Entered or derived**	**Comment**
AF-AFP level flag	Specifies if the MS-AFP measurement was below the entered value	Text(1)	✗	✓	✗	✗	-	Derived	
AF-AFP MoM flag	Specifies if the marker MS-AFP MoM was below the value shown	Text(1)	✗	✓	✗	✗	-	Derived	
Age at EDD (decimal)	Age at expected date of delivery (calculated with decimal fraction)	Single	✗	✓	✓	✗	-	Derived	Years and decimal fraction

NOTES

1. Fields

For fields labelled * the alternative wording chosen by the user (if provided) will be used in the list of available fields.
Only fields in the data entry screen will appear in the import or export specification.
For import, fields shaded yellow (grouped fields) must all be blank or all be completed. Fields can be imported in any order except for the grouped fields.

2. Marker names and numbers

Marker numbers 4 to 12 are replaced by the name of the corresponding marker used in **αlpha**.

3. Date and time formats

The date format is as specified in the import, export or data transfer format specification (dd/mm/yy, mm/dd/yy or yy/mm/dd)

Time format is hh:mm:ss

For importing data, if the file format is comma separated or tab separated, the date should be provided with separators and leading zeroes. For example 9 April 2010 in Day/Month/Year format would be imported as 09/04/10. If the file format is fixed length, the date should be provided in 3I2 format. For example 9 April 2010 in Day/Month/Year format would be imported as 090410.

4. Text (x)
Data is imported and exported as text with the maximum number of characters given by x. Imported data greater than x characters length is truncated to x characters.

5. Integer & Long Integer

Data is exported as an integer value (between – 32,768 and 32,767)

Data is exported as a long integer (between – 2,147,483,648 and 2,147,483,647)

6. Single

Data is exported as a floating point number (– 3.402823E38 to – 1.401298E-45 for negative values, 1.401298E-45 to 3.402823E38 for positive values, and 0)

7. blank values (comma separated and tab separated file formats)

If there is no value for a field, the corresponding field in the data transfer, import or export file is blank. A blank field is shown by one field separator immediately following another. For example if the fields:

field1, field2,field3

are exported with values:

value1, blank value,value3

the file will contain (when the separator is a comma):

value1,,value3

8. Regional settings using "," as the decimal separator and "." as the thousands separator

8.1 Data transfer:

If the data transfer field separator is a comma numbers are exported with "." as the decimal separator.

If the data transfer field separator is a tab or the file is in fixed width format numbers are exported with "," as the decimal separator.

Exported numbers do not use a thousand's separator.

8.2 Import and Export

If the import or export format field separator is a comma numbers are imported and exported with "." as the decimal separator.

If the import or export format field separator is a tab or fixed length format is used numbers are imported or exported with "," as the decimal separator.

Imported and exported numbers do not use the thousand's separator.

9 Excel cell formats for Analyze-it

The fields are exported to Excel cells with the following formats:

Export field	**Excel cell format**
Integer, long integer and single	General (Numbers will be formatted using the regional settings used in Windows)
Text (x) (x is the maximum number of characters in the text string)	General
Date and time	Date (Dates will be formatted according to the regional settings used in Windows)
NULL	Blank cell

10. Gestational age format

The gestational age is entered in weeks and days including the separator. For example 16 weeks 3 days is entered as "16+3". For the comma separated variable file format the "+" separator must be used.

11 NT levels

11.1 Data transfer

For twins, the levels corresponding to the marker number for NT will be expanded to a separate field for each fetal measurement.

11.2 Analyze-it

For NT the level is given as a 3 digit number followed by a slash (x.xx/) or for a twin pregnancy two 3 digit numbers separated by a slash (x.xx/y.yy)

11.3 Import/Export

NT levels are imported and exported according to the setting of the **Import NT levels to 2 dp mode** on the Import Data Format screen and **Export NT levels to 2 dp mode** on the **Export Settings** screen (Section 3.9)

Import/Export NT levels to 2 dp mode	**Fixed length format**	**Singleton**	**Twin**
NOT SET	A6	The NT level is a 3-digit number between 0.1 and 9.9 In fixed length format a value is entered, for example, as 1.6 followed by three spaces.	The NT levels are two 3-digit numbers between 0.1 and 9.9, without separators e.g. “1.61.2”
SET	A8	The NT level is a 4-digit number between 0.01 and 9.99 In fixed length format a value is entered, for example as 1.65 followed by four spaces.	The NT levels are two 4-digit numbers between 0.01 and 9.99, without separators e.g. “1.651.25”

12. Import/Export Format : DOS Compatibility mode

If **DOS compatible mode** is selected in the MS Import Data Format or MS Export Data Format screen, the doctor, address code and sonographer code are taken to be four characters long and the fixed length formats are A15, A4 and I4.4 respectively.

See also section 15.3.

13. Importing data for the Integrated test

When importing data for the integrated test using the import data format, it is necessary to send all the data (relating to both the samples) in one record. Once imported, a record cannot be updated with subsequent information using this method. For this reason, the demographic and first sample data should be held on the 'host' system until the second sample data are available, after which all the data can be sent to **αlpha**.

When only demographic information and first trimester data have been imported into **αlpha** using this method and this data is held in a batch file (and so not yet final reported) , the second trimester results may be imported into **αlpha** using the **analyser import** feature (Section 3.10)

14. Risks (post) (Export only)

For comma separated and fixed length export posterior risks are reported in the format:

<left hand side of risk>, <right hand side of risk>

The table below shows examples of how the risk is exported:

Risk on screening report	Value in export file
1 in 100	1,100
4 in 5	4,5
Greater than 9 in 10	>9,10
Less than 1 in 1,000,000	<1, 1000000

For tab separated format a tab character is always used as the separator between the left and right hand side of the posterior risks.

15. NT MoM values

15.1 Data transfer

For twins, the MoM values corresponding to the marker number for NT will be expanded to a separate field for the NT MoM value for each fetus.

15.2 Analyze-it

For twins, the MoM values corresponding to the marker number for NT will be expanded to a separate field for the NT MoM value for each fetus.

15.3 Export

Fixed Length Format	Comma separated		Tab separated	
Singleton and twin	**Singleton**	**Twin**	**Singleton**	**Twin**
A10	Real number with two digits after the decimal point	In a twin pregnancy, if two NT measurements are recorded, two MoMs are exported each in a fixed field of five characters, for example: '1.10 0.96 '	Real number with two digits after the decimal point followed by a blank field (ie an additional tab character) If NT MoMs are not calculated two blank fields separated by a tab are exported.	In a twin pregnancy, if two NT measurements are recorded, the MoMs are exported as two real numbers separated by a tab each with two digits after the decimal point

In **DOS compatible mode** the MoMs in a twin pregnancy are exported as two real numbers separated by a "/" each with two digits after the decimal point.

16. Reason codes for positive and uninterpretable results (maternal serum)

Reason code	Meaning			
A	Uninterpretable (test done too early)			
B	Uninterpretable (test done too late)			
C	Uninterpretable (grand multiple pregnancy)			
D	Uninterpretable (amniocentesis attempted before blood sample)			
E	Uninterpretable (diabetes and twin pregnancy)			
F				IRDS
G			RAFP	
H			RAFP	IRDS
I		PNTD		
J		PNTD		IRDS
K		PNTD	RAFP	
L		PNTD	RAFP	IRDS
M	PDS			
N	PDS			IRDS
O	PDS		RAFP	
P	PDS		RAFP	IRDS
Q	PDS	PNTD		
R	PDS	PNTD		IRDS
S	PDS	PNTD	RAFP	
T	PDS	PNTD	RAFP	IRDS
Codes F through T correspond to positive screening results, and show the possible combinations of reasons for a positive result. PDS Previous Down's syndrome pregnancy PNTD Previous NTD pregnancy				

RAFP	Raised AFP
IRDS	Increased risk of Down's syndrome

Codes 16 through 63 correspond to positive screening results when the interpretation involves pre-eclampsia.

Reason code	Previous pre-eclampsia	Increased risk of pre-eclampsia	Previous Down's syndrome	Previous NTD	Raised AFP	Increased risk of Down's syndrome
16		Yes				
17		Yes				Yes
18		Yes			Yes	
19		Yes			Yes	Yes
20		Yes		Yes		
21		Yes		Yes		Yes
22		Yes		Yes	Yes	
23		Yes		Yes	Yes	Yes
24		Yes	Yes			
25		Yes	Yes			Yes
26		Yes	Yes		Yes	
27		Yes	Yes		Yes	Yes
28		Yes	Yes	Yes		
29		Yes	Yes	Yes		Yes
30		Yes	Yes	Yes	Yes	
31		Yes	Yes	Yes	Yes	Yes
32	Yes					
33	Yes					Yes
34	Yes				Yes	
35	Yes				Yes	Yes
36	Yes			Yes		
37	Yes			Yes		Yes
38	Yes			Yes	Yes	
39	Yes			Yes	Yes	Yes
40	Yes		Yes			
41	Yes		Yes			Yes
42	Yes		Yes		Yes	
43	Yes		Yes		Yes	Yes
44	Yes		Yes	Yes		
45	Yes		Yes	Yes		Yes
46	Yes		Yes	Yes	Yes	
47	Yes		Yes	Yes	Yes	Yes
48	Yes	Yes				
49	Yes	Yes				Yes
50	Yes	Yes			Yes	
51	Yes	Yes			Yes	Yes
52	Yes	Yes		Yes		
53	Yes	Yes		Yes		Yes
54	Yes	Yes		Yes	Yes	
55	Yes	Yes		Yes	Yes	Yes
56	Yes	Yes	Yes			
57	Yes	Yes	Yes			Yes
58	Yes	Yes	Yes		Yes	
59	Yes	Yes	Yes		Yes	Yes

Reason code	Previous pre-eclampsia	Increased risk of pre-eclampsia	Previous Down's syndrome	Previous NTD	Raised AFP	Increased risk of Down's syndrome
60	Yes	Yes	Yes	Yes		
61	Yes	Yes	Yes	Yes		Yes
62	Yes	Yes	Yes	Yes	Yes	
63	Yes	Yes	Yes	Yes	Yes	Yes

Reason codes for positive and uninterpretable results (amniotic fluid)

Reason code	Meaning
A	Uninterpretable (test done too early)
B	Uninterpretable (test done too late)
C	Positive (raised AF-AFP)
D	Positive (raised AF-AFP and AChE band present)
E	Ambiguous (raised AF-AFP and AChE band absent)
F	Ambiguous (AChE band present and AF-AFP not raised)

Appendix H Definitions and abbreviations

95% confidence interval	The range of values within which one can be 95% certain that the true value occurs. If the same trial were repeated 100 times, in 95 trials the confidence interval would include the true value, and in 5 trials it would not
a*b	a multiplied by b
ab**	a raised to the power b
AC	Abdominal circumference
AChE	Acetylcholinesterase
AChE NTD band	The amniotic fluid electrophoretic gel band that migrates to the same position as cerebrospinal fluid and is inhibited by BW284C51
AF	Amniotic fluid
AFP	Alpha-fetoprotein
Anencephaly	Anencephaly with or without spina bifida
BPD	Biparietal diameter
Clinical GA	**GA** based on clinical examination
Combined Test	Late first trimester (10-13 completed weeks) test based on combining **NT** measurement with **hCG**, **PAPP-A** and maternal age
CRL	Crown-rump length
Dates GA	**GA** based on time since the first day of **LMP**
Detection rate	The proportion of affected pregnancies with positive screening results
Double Test	Early second trimester (14-22 completed weeks) test based on the measurement of **AFP** and **hCG** together with maternal age
DVPI	Ductus venosus pulsatility index
EDC	Expected date of confinement
EDD	Expected date of delivery
False-positive rate	The proportion of unaffected pregnancies with positive screening results
GA	Gestational age. This is usually reported in weeks and days and grouped in completed weeks. (For example, 16 completed weeks includes 16 weeks to 16 weeks 6 days).
HC	Head circumference
hCG	Human chorionic gonadotrophin
ID Code	A unique personal identifier (Medicare No., Hospital No., National Health Service No.)
Integrated Test	The use of screening markers measured in the first and second trimester of pregnancy integrated into a single test result. Unless otherwise qualified, 'Integrated Test' refers to the integration of **NT** measurement and **PAPP-A** in the first trimester with the **Quadruple Test** in the second
LMP	First day of last menstrual period
MA	Maternal age
MS	Maternal serum
MoM	Multiple of the median value of a screening marker in unaffected pregnancies of the same gestational age measured in the same laboratory (or in the case of ultrasound measurements at the same centre or by the same sonographer). It

	is therefore the observed concentration divided by the expected concentration where the expected is the median. The median is often calculated using measurements from all pregnancies (not just unaffected pregnancies); this makes little or no difference to estimating the MoM value because affected pregnancies are rare and therefore have little or no influence on the median. The MoM allows for the change in concentrations of the serum markers with gestation and from centre to centre.
m/s	Metres per second
NT	Nuchal translucency
NTD	Neural tube defect
Open spina bifida	Spina bifida with neural tissue either completely exposed or covered by a thin transparent membrane
OC	Oral contraceptives
PAPP-A	Pregnancy associated plasma protein A
PChE	Pseudocholinesterase
PlGF	Placental growth factor
Quadruple Test	Early second trimester (14-22 completed weeks) test based on the measurement of **AFP**, **uE3**, **total hCG** and inhibin-A together with maternal age
RBC	Red blood cells
Scan GA	**GA** based on ultrasound examination
Sequential Testing	Testing in which a first-trimester test is performed (for example the **Combined test**) and the results interpreted immediately. If this is positive, a diagnostic test is offered, but if it is not positive, second trimester serum markers are measured and the first trimester markers reused to form an **Integrated Test.**
Serum Integrated Test	A variant of the **Integrated Test** using serum markers only (**PAPP-A** in the first trimester and the **Quadruple Test** in the second trimester
SLOS	Smith-Lemli-Opitz syndrome
Spina bifida	Spina bifida cystica or encephalocele without anencephaly
Triple Test	Early second trimester (14-22 completed weeks) test based on the measurement of **AFP**, **uE3** and **hCG** together with maternal age
uE_3	Unconjugated oestriol
XPS	XML Paper Specification. A file format in common use for the exchange of printable documents.

Appendix I Packet export report format

When final reports are exported as packeted information, the principle is to split each item in the report into two parts, an invariable first part (for example, **Surname**) and a variable second part (for example, **SMITH**). Some items consist of only one part (for example, **$025 This is a repeat test**). In these items, the second part is taken to be empty.

Each item has a unique code. The codes and the items they correspond to are described in the following table:

Code	First part of item
$005	NEURAL TUBE DEFECT AND DOWN'S SYNDROME SCREENING*
$006	AMNIOTIC FLUID AFP*
$010	This is a corrected version of the report produced on <date>
$015	This is a reinterpretation of the report produced on <date> following the addition of further information
$020	A repeat test was requested but no previous test for this pregnancy has been found. It has therefore been interpreted as a first test
$025	This is a repeat test
$030	Surname
$035	Forename(s)
$040	Address
$045	Phone number
$050	ID Code
$055	Date of birth
$060	LMP
$065	EDD (based on LMP)
$066	EDD (based on ultrasound)
$067	EDD (if no other EDD entered)
$070	Date of sample (first sample in integrated screening)
$071	Date of second sample (in integrated screening only)
$075	Date received
$080	Time received
$085	Lab Number
$090	Doctor
$095	Report Address
$100	Spare (1)
$105	Spare (2)
$110	Spare (3)
$115	Spare (4)
$116	Spare (5)
$117	Spare (6)
$120	Previous NTD
$125	Previous Down's
$126	Age at previous pregnancy affected by Down's syndrome
$127	Previous pre-eclampsia
$128	Ductus venosus blood flow
$130	Insulin dependent diabetes mellitus
$131	Smoker

Code	First part of item	
$132	IVF pregnancy	
$133	Date of egg collection	
$134	Date of embryo transfer	
$135	Maternal Age at EDD	
$136	Donor age at EDD	
$140	Reason for amniocentesis	
$145	Ultrasound Scan	
$150	Scan Measurement	
$155	Scan Measure	
$160	Gestation at Date of Sample (non-Integrated Test)	
$161	Gestation at date of 1st sample (integrated screening only)	
$162	Gestation at date of 2nd sample (integrated screening only)	
$165	Weight	
$170	Ethnic group	
$175	Sample Appearance	
$180	Fetal cells (%)	
$185	RBC (million/ml)	
$187	Fetal Nasal Bone	
$190	Marker 1 (MS-AFP)	
$195	Marker 2 (uE_3)	
$200	Marker 3 (total hCG)	
$201-$203	Markers 4-6. The identities of the markers can be determined from the 4th, 5th and 6th entries in the **Markers** screen (Section 3.13)	
$205	AF-AFP Level	
$206-$209	Markers 7-10. The identities of the markers can be determined from the 7th, 8th , 9th and 10th entries in the **Markers** screen (Section 3.13)	
$210	AChE NTD Bands	
$211-$212	Markers 11-12. The identities of the markers can be determined from the 11th and 12th entries in the **Markers** screen (Section 3.13)	
$215	PChE Bands	
$220	It is no longer possible to reprint this report in full, because links with other reports were changed as a result of the correction on <report date>	
$225	Screening result	
$230	Diagnostic result	
$235	Reason	
$240	Comment	
$245	Risk of Down's	
$255	Risk of pre-eclampsia	
$250	Risk of NTD	
$260	PREVIOUS REPORTS REPORT SAMPLE TEST RESULT NOTES	
$265	Fixed text portion of window envelope	
$270	Gestation used	
$275	Positive and negative footnotes	
$280	Title for MS message addition system	
$285	MS message addition	Header message
$290		Footer
$295		Missing weight

Code	First part of item
$300	Missing diabetes
$305	Missing ethnic group
$310	Missing previous Down's syndrome
$315	Missing previous NTD
$320	Clinical gestation only
$325	Twin pregnancy
$330	Screen negative – first test
$335	Screen negative – repeat test
$340	Screen positive NTD – raised AFP, first test with scan
$345	Screen positive NTD – raised AFP, first test without scan
$350	Screen positive NTD – raised AFP, repeat test
$355	Screen positive NTD – previous NTD
$360	Screen positive Down's – increased Down's risk, first test with scan
$365	Screen positive Down's – increased Down's risk, first test without scan
$370	Screen positive Down's – increased Down's risk, repeat test
$375	Screen positive Down's – previous Down's syndrome
$380	Age at EDD > specified level
$385	MS-AFP >= specified level – first test with scan
$390	MS-AFP >= specified level – first test without scan
$395	MS-AFP >= specified level – repeat test
$400	MS-AFP <= specified level – first test with scan
$405	MS-AFP <= specified level – first test without scan
$410	MS-AFP <= specified level – repeat test
$415	MS-AFP between specified levels – first test with scan
$420	MS-AFP between specified levels – first test without scan
$425	MS-AFP between specified levels – repeat test
$430	Increased risk of T18
$435	Test at 14 weeks
$440	Weight >= specified weight
$445	Increased risk of SLOS

$380	Title for AF message addition system

Code	First part of item	
$385	AF message addition	Header message
$390		Footer message
$395		Negative
$400		Positive (↑ AFP)
$405		Positive (↑ AFP and positive AChE)
$410		Ambiguous (↑ AFP and negative AChE)
$415		Ambiguous (↓ AFP and positive AChE)

* The second part is “Report dated <date>”

Format of packeted items

An item with code $N appears in the exported file of reports as a string (the packet header):

```
$N,n1,n2,n3
```

followed by n3 lines (of maximum length 80 characters, terminated by a carriage return and line feed), n1 lines being the first part of the item and the next n2 lines the second part.

Each line of the first part is delimited by ? and each line of the second part by /.

The numbers n1, n2 and n3 are two digits, packed with a leading zero as necessary. For example:

```
$030,01,01,02
?Surname?
/SMITH/
```

Multiple patients in a batch

Screening reports are normally processed in a batch containing many patients. In this case the packeted export file will contain the results of all the patients, with each new patient starting with the $005 packet.

Example of report in Packet Format

The following shows the report in Figure 5 in Packet Export Format

```
$090,00,01,01
/Dr Albert Brown MD/
$095,00,04,04
/The Surgery/
/24 Park Lane/
/LONDON/
/NE3 ZA9/
$005,01,01,02
?DOWN'S SYNDROME, NEURAL TUBE DEFECT AND PRE-ECLAMPSIA SCREENING?
/Report dated 08 Jan 14/
$030,01,01,02
?Last name?
/JONES/
$035,01,01,02
```

```
?Forename(s)?
/Jenny/
$050,01,01,02
?Hospital Number?
/1342ZYD/
$055,01,01,02
?Date of birth?
/02/03/82/
$060,01,01,02
?LMP?
/10/09/13/
$067,01,01,02
?EDD?
/20/06/14/
$070,01,01,02
?Date of sample?
/07/12/13/
$071,01,01,02
?Date of 2nd sample?
/07/01/14/
$085,01,01,02
?Sample number 1?
/52413/
$100,01,01,02
?Sample number 2?
/52601/
$120,01,01,02
?Previous NTD?
/None/
$125,01,01,02
?Previous Down's?
/None/
$127,01,01,02
?Prev. Pre-eclampsia?
/No/
$130,01,01,02
?Insulin dependent diabetes?
/None/
$131,01,01,02
?Smoker?
/No/
$135,01,01,02
?Maternal age at EDD?
/32 years/
$150,01,01,02
?Scan measurement (CRL)?
/55.4 mm on 07/12/13/
$161,01,02,03
?Gestation at date of 1st sample?
/12 weeks 4 days (by dates)/
/12 weeks 1 days (by CRL scan)/
$162,01,02,03
?Gestation at date of 2nd sample?
/17 weeks 0 days (by dates)/
/16 weeks 4 days (by CRL scan)/
$270,01,01,02
?Gestation used?
/Scan estimate (CRL)/
$165,01,01,02
?Weight?
/65.2 kg/
$170,01,01,02
?Ethnic group?
/Caucasian/
$190,01,01,02
?MS-AFP level?
```

```
/30.1 ng/mL    0.77 MoM/
$195,01,01,02
?uE3 level?
/2.1 ng/mL     0.75 MoM/
$200,01,01,02
?Total hCG level?
/21000 miu/mL  1.27 MoM/
$202,01,01,02
?Inhibin-A level?
/210.1 pg/mL   0.96 MoM/
$203,01,01,02
?Nuchal measurement?
/1.2 mm        0.96 MoM/
$206,01,01,02
?PAPP-A level?
/12.11 mg/L    1.10 MoM/
$225,01,01,02
?Screening result?
/Screen negative/
$245,01,01,02
?Risk of Down's?
/1 in 9,000 (at term)/
$250,01,01,02
?Risk of NTD?
/1 in 7,000/
$255,01,01,02
?Risk of Pre-eclampsia?
/1 in 60/
$240,01,01,02
?Comment?
/Down's risk due to maternal age alone is 1 in 720/
$240,01,01,02
?Comment?
/Not in the high risk category for trisomy 18 (risk < 1 in 100)/
$240,01,01,02
?Comment?
/Not in the high risk category for trisomy 13 (risk < 1 in 100)/
$275,00,03,03
/A screen negative result does not exclude the possibility of Down's syndrome,/
/a neural tube defect or pre-eclampsia, because screening does not detect all/
/affected pregnancies/
```

Appendix J Statistical parameters: Down's syndrome

The age-specific live birth prevalence of Down's syndrome is given by[46,55]:

$$prevalence = \frac{1}{1+e^{7.33-4.211/\left(1+e^{-0.2815(age-37.23)}\right)}}$$

The risk of an individual woman having a pregnancy affected with Down's syndrome is given by[74]:

$$risk = \frac{1}{1+e^{7.33-4.211/\left(1+e^{-0.2815(age-37.73)}\right)}}$$

Where *age* is the woman's age in years at the expected date of delivery.

Median screening marker levels (log_{10} MoM) in Down's syndrome pregnancies according to gestational age

Gestational age		Median †							
Week	Day	NT [53]	PAPP-A [49]	Total hCG [49]	Freeß hCG [49]	PlGF [91]	AFP [49]	uE_3 [49]	Inhibin-A [49]
10	0	0.4027	-0.4689	-0.0171	0.2105	n/a	n/a	n/a	n/a
	1	0.3962	-0.4593	-0.0050	0.2182				
	2	0.3897	-0.4496	0.0072	0.2259				
	3	0.3833	-0.4400	0.0193	0.2335				
	4	0.3768	-0.4303	0.0314	0.2412				
	5	0.3703	-0.4207	0.0436	0.2489				
	6	0.3639	-0.4110	0.0557	0.2566				
11	0	0.3574	-0.4014	0.0678	0.2643	-0.0403	n/a	n/a	n/a
	1	0.3509	-0.3917	0.0799	0.2719	-0.0507			
	2	0.3444	-0.3821	0.0921	0.2796	-0.0610			
	3	0.3380	-0.3724	0.1042	0.2873	-0.0714			
	4	0.3315	-0.3628	0.1163	0.2950	-0.0817			
	5	0.3250	-0.3531	0.1285	0.3027	-0.0921			
	6	0.3186	-0.3435	0.1406	0.3103	-0.1025			
12	0	0.3121	-0.3338	0.1527	0.3180	-0.1128	n/a	n/a	n/a
	1	0.3056	-0.3242	0.1649	0.3257	-0.1232			
	2	0.2992	-0.3145	0.1770	0.3334	-0.1335			
	3	0.2927	-0.3049	0.1891	0.3411	-0.1439			
	4	0.2862	-0.2952	0.2012	0.3487	-0.1543			
	5	0.2798	-0.2856	0.2134	0.3564	-0.1646			
	6	0.2733	-0.2759	0.2255	0.3641	-0.1750			
13	0	0.2668	-0.2663	0.2376	0.3718	-0.1853	n/a	n/a	n/a
	1	0.2604	-0.2566	0.2498	0.3795	-0.1957			
	2	0.2539	-0.2470	0.2619	0.3871	-0.2061			
	3	0.2474	-0.2373	0.2740	0.3948	-0.2164			
	4	0.2410	-0.2277	0.2862	0.4025	-0.2268			
	5	0.2345	-0.2180	0.2983	0.4102	-0.2371			
	6	0.2280	-0.2084	0.3104	0.4179	-0.2475			
14-22	n/a	n/a	n/a	0.3118	0.4249	n/a	-0.1308	-0.1549	0.3384

† Unaffected means set to 0
n/a Not applicable

The median DVPI MoM in Down's syndrome pregnancies = 0.1903 (11 – 13 weeks)[81]

The regression equations used to estimate the biochemical marker median in affected pregnancies in the first trimester are:

median total hCG = $10^{-0.8662 + 0.01213 \times \text{gestational age in days } 49}$
median free β-hCG = $10^{-0.3271 + 0.00768 \times \text{gestational age in days } 49}$
median PAPP-A = $10^{-1.1444 + 0.00965 \times \text{gestational age in days } 49}$
median PlGF = $10^{0.7573536 - 0.0103592 \times \text{gestational age in days } 91}$

The regression equation used to estimate the NT median in affected pregnancies is [53]:
median NT (MoM) = $10^{0.8554679 - .0064686 \times \text{gestational age in days}}$

N.B. There are intellectual property rights covering the use of screening markers and screening tests (e.g. the Integrated Test), and users need to ensure that they have the right to use them.

Standard deviations of the screening markers (log_{10} MoM) in each trimester of pregnancy [49]

		Gestational age based on			
		Dates		Scan	
Maternal weight correction		No	Yes	No	Yes
Down's syndrome					
First trimester (10-13 weeks)					
NT		-	-	0.2313	0.2313
PAPP-A		0.3161	0.2959	0.3006	0.2802
Total hCG		0.2202	0.2111	0.2151	0.2069
Free ß hCG		0.2651	0.2637	0.2587	0.2569
DVPI[81]		0.1705	0.1705	0.1705	0.1705
PlGF[91]		0.1955	0.1955	0.1955	0.1955
Second trimester (14-22 weeks)					
AFP		0.1497	0.1416	0.1485	0.1398
uE_3		0.1377	0.1370	0.1251	0.1238
Total hCG		0.2424	0.2397	0.2422	0.2395
Free ß hCG		0.3020	0.2996	0.2987	0.2965
Inhibin-A		0.2249*	0.2213*	0.2249*	0.2213[88]
Unaffected					
First trimester (10-13 weeks)					
NT	10 weeks[75]	-	-	0.1550	0.1550
	11 weeks[75]	-	-	0.1275	0.1275
	12-13 weeks[75]	-	-	0.1105	0.1105
PAPP-A		0.2893	0.2670	0.2722	0.2495
Total hCG		0.2091	0.1994	0.2037	0.1950
Free ß hCG		0.2731	0.2718	0.2669	0.2651
DVPI[81]		0.0757	0.0757	0.0757	0.0757
PlGF[91]		0.1556	0.1556	0.1556	0.1556
Second trimester (14-22 weeks)					
AFP		0.1498	0.1417	0.1486	0.1399
uE_3		0.1292	0.1284	0.1156	0.1142
Total hCG		0.2307	0.2279	0.2305	0.2276
Free ß hCG		0.2639	0.2612	0.2602	0.2577
Inhibin-A		0.1828*	0.1779*	0.1828*	0.1779[88]

* Jon Bestwick, personal communication.

Truncation limits (MoM) for Down's syndrome screening markers

Marker	Truncation limits†
NT [75]	
10 completed weeks	0.50 – 2.50
11 completed weeks	0.70 – 2.50
12 completed weeks	0.80 – 2.50
13 completed weeks	0.85 – 2.50
First trimester (10-13 weeks) [49]	
PAPP-A	0.2 – 3.0
Total hCG	0.3 – 3.0
Free ß hCG	0.3 – 5.0
DVPI[81]	0.9 – 1.5
PlGF[91]	0.4 - 2.5
Second trimester (14-22 weeks)	
AFP[88]	0.5 – 2.5
uE_3[49]	0.4 – 2.0
Total hCG[49]	0.4 – 5.0
Free ß hCG[49]	0.3 – 5.0
Inhibin-A[49]	0.3 – 5.0

† For MoM values outside the specified range, the risk is estimated for the corresponding limit

Adjustment for recurrent false positive screening results[50 59]

The expected MoM in current pregnancy = Previous Pregnancy MoM [b]

Values of the exponent b are given in the following table:

First trimester	b
PAPP-A	0.42
Free ß hCG	0.49
Second trimester	**b**
AFP	0.41
uE3	0.26
Total hCG	0.42
Free ß hCG	0.42
Inhibin-A	0.40

Correlation coefficients for the screening markers in *unaffected pregnancies* (gestational age based on dates, without adjustment for maternal weight [49] **(Unless stated otherwise)**

	First Trimester				Second trimester			
	Total hCG	Free β-hCG	PAPP-A	PlGF	AFP	uE_3	Total hCG	Free β-hCG
First trimester								
Free β-hCG	0.7023							
PAPP-A	0.2067	0.1315						
PlGF		0.1526[91]	0.2860[91]					
DVPI	0.0000[81]	-0.0285[81]	0.0269[81]					
Second trimester								
AFP	0.1085	0.0571	0.2461	-0.1477[91]				
uE_3	0.0044	-0.0479	0.2820	-0.0547[91]	0.2595			
Total hCG	0.7050	0.5667	0.0816		0.1781	-0.0825		
Free β-hCG	0.6968	0.7494	0.0692	-0.0854[91]	0.1168	-0.0904	0.8607	
Inhibin-A	0.3295	0.3094	0.0652	-0.1509[91]	0.2293	-0.0876	0.4412	0.4122

Correlation coefficients for the screening markers in *unaffected pregnancies* (gestational age based on dates, with adjustment for maternal weight[49] **(Unless stated otherwise)**

	First trimester				Second trimester			
	Total hCG	Free β-hCG	PAPP-A	PlGF	AFP	uE_3	Total hCG	Free β-hCG
First trimester								
Free β-hCG	0.6953							
PAPP-A	0.1490	0.0763						
PlGF		0.1526[91]	0.2860[91]					
DVPI	0.0000[81]	-0.0285[81]	0.0269[81]					
Second trimester								
AFP	0.0481	0.0048	0.1728	-0.1477[91]				
uE_3	-0.0162	-0.0654	0.2776	-0.0547[91]	0.2473			
Total hCG	0.7010	0.5401	0.0214		0.1336	-0.1008		
Free β-hCG	0.6967	0.7292	0.0127	-0.0854[91]	0.0722	-0.1089	0.8475	
Inhibin-A	0.3095	0.2852	0.0030	-0.1509[91]	0.1896	-0.1083	0.4225	0.3957

Correlation coefficients for the screening markers in *unaffected pregnancies* (gestational age based on scan, without adjustment for maternal weight [49] **(Unless stated otherwise)**

	First trimester							Second trimester			
	NT (10 weeks)	NT (11 weeks)	NT (12-13 weeks)	Total hCG	Free β-hCG	PAPP-A	PlGF	AFP	uE_3	Total hCG	Free β-hCG
First trimester											
Total hCG	-0.0626	-0.0753	-0.0815								
Free β-hCG	-0.0334	-0.0402	-0.0436	0.7281							
PAPP-A	-0.0417	-0.0503	-0.0544	0.2795	0.1961						
PlGF	-0.0093[91]	-0.0093[91]	-0.0093[91]		0.1526[91]	0.2820[91]					
DVPI	0.0714[81]	0.0714[81]	0.0714[81]		-0.0285[81]	0.0269[81]					
Second trimester											
AFP	-0.0097	-0.0116	-0.0126	0.1298	0.0736	0.2105	-0.1477[91]				
uE_3	0.0476	0.0573	0.0621	0.0572	-0.0023	0.1533	-0.0547[91]	0.2219			
Total hCG	-0.0556	-0.0669	-0.0725	0.7225	0.5858	0.1217		0.1939	-0.0193		
Free β-hCG	-0.0507	-0.0610	-0.0660	0.7258	0.7781	0.1186	-0.0854[91]	0.1417	-0.0357	0.8764	
Inhibin-A	-0.0414	-0.0499	-0.0540	0.3366	0.3179	0.0877	-0.1509[91]	0.2411	-0.0627	0.4441	0.4242

Correlation coefficients for the screening markers in *unaffected pregnancies* (gestational age based on scan, with adjustment for maternal weight [49] **(Unless stated otherwise)**

	First trimester							Second trimester			
	NT (10 weeks)	NT (11 weeks)	NT (12-13 weeks)	Total hCG	Free β-hCG	PAPP-A	PlGF	AFP	uE_3	Total hCG	Free β-hCG
First trimester											
Total hCG	-0.0630	-0.0758	-0.0821								
Free β-hCG	-0.0325	-0.0391	-0.0423	0.7178							
PAPP-A	-0.0429	-0.0516	-0.0559	0.2198	0.1395						
PlGF	0.0093[91]	0.0093[91]	0.0093[91]		0.1526[91]	0.2820[91]					
DVPI	[1]	[1]	[1]		-0.0285[81]	0.0269[81]					
	0.0714[81]	0.0714[81]	0.0714[81]								
Second trimester	[1]	[1]	[1]								
AFP				0.0675	0.0167	0.1160	-0.1477[91]				
uE_3				0.0306	-0.0255	0.1213	-0.0547[91]	0.1981			
Total hCG				0.7191	0.5606	0.0624		0.1535	-0.0416		
Free β-hCG	-0.0079	-0.0095	-0.0103	0.7236	0.7605	0.0627	-0.0854[91]	0.0974	-0.0585	0.8651	
Inhibin-A	0.0495	0.0596	0.0645	0.3167	0.2937	0.0237	-0.1509[91]	0.2033	-0.0875	0.4293	0.4092
	-0.0549	-0.0661	-0.0716								
	-0.0502	-0.0604	-0.0654								
	-0.0415	-0.0499	-0.0540								

Correlation coefficients for the screening markers in *Down's syndrome pregnancies* (gestational age based on dates, without adjustment for maternal weight [49] **(Unless stated otherwise)**

	First trimester				Second trimester			
	Total hCG	Free β-hCG	PAPP-A	PlGF	AFP	uE_3	Total hCG	Free β-hCG
First trimester								
Free β-hCG	0.5115							
PAPP-A	0.1330	-0.0456						
PlGF		-0.0651[91]	0.0424[91]					
DVPI		0.0000[81]	0.0000[81]					
Second trimester								
AFP	0.1416	0.1063	0.1945	-0.2692[91]				
uE_3	-0.1656	-0.3446	0.4586	-0.0056[91]	-0.0017			
Total hCG	0.6809	0.4695	-0.1761		0.2121	-0.3796		
Free β-hCG	0.5605	0.7675	-0.2484	-0.3058[91]	0.2060	-0.4172	0.8160	
Inhibin-A	0.2618	0.3031	-0.1282	-0.0053[91]	0.1976	-0.2989	0.4296	0.4394

Correlation coefficients for the screening markers in *Down's syndrome pregnancies* (gestational age based on dates, with adjustment for maternal weight [49] **(Unless stated otherwise)**

	First trimester				Second trimester			
	Total hCG	Free β-hCG	PAPP-A	PlGF	AFP	uE_3	Total hCG	Free β-hCG
First trimester								
Free β-hCG	0.4929							
PAPP-A	0.0749	-0.1112						
PlGF		-0.0651[91]	0.0424[91]					
DVPI		0.0000[81]	0.0000[81]					
Second trimester								
AFP	0.0879	0.0554	0.1211	-0.2692[91]				
uE_3	-0.1921	-0.3646	0.4671	-0.0056[91]	-0.0288			
Total hCG	0.6758	0.4418	-0.2487		0.1725	-0.4008		
Free β-hCG	0.5551	0.7494	-0.3170	-0.3058[91]	0.1738	-0.4366	0.8046	
Inhibin-A	0.2442	0.2824	-0.1879	-0.0053[91]	0.1661	-0.3182	0.4148	0.4284

Correlation coefficients for the screening markers in *Down's syndrome pregnancies* (gestational age based on scan, without adjustment for maternal weight [49] **(Unless stated otherwise)**

	First trimester					Second trimester			
	NT	Total hCG	Free β-hCG	PAPP-A	DVPI	AFP	uE_3	Total hCG	Free β-hCG
First trimester									
Total hCG	-0.0804								
Free β-hCG	0.1063	0.5272							
PAPP-A	-0.1420	0.1894	0.0004						
PlGF	0.0134[91]		-0.0651[91]	0.0424[91]					
DVPI	0.3855[81]		0.0000[81]	0.0000[81]					
Second trimester									
AFP	0.0744	0.1627	0.1250	0.1580	-0.2692[91]				
uE_3	0.0679	-0.1410	-0.3387	0.3788	-0.0056[91]	-0.0670			
Total hCG	0.0451	0.6960	0.4869	-0.1552		0.2276	-0.3540		
Free β-hCG	0.1454	0.5803	0.7955	-0.2293	-0.3058[91]	0.2294	-0.4106	0.8279	
Inhibin-A	0.1818	0.2668	0.3117	-0.1217	-0.0053[91]	0.2069	-0.3035	0.4319	0.4485

Correlation coefficients for the screening markers in *Down's syndrome pregnancies* (gestational age based on scan, with adjustment for maternal weight[49] **(Unless stated otherwise)**

	First trimester				Second trimester				
	NT	Total hCG	Free β-hCG	PAPP-A	DVPI	AFP	uE_3	Total hCG	Free β-hCG
First trimester									
Total hCG	-0.0819								
Free β-hCG	0.1080	0.5053							
PAPP-A	-0.1506	0.1284	-0.0692						
PlGF	0.0134[91]		-0.0651[91]	0.0424[91]					
DVPI	0.3855[81]		0.0000[81]	0.0000[81]					
Second trimester									
AFP	0.0809	0.1075	0.0697	0.0660	-0.2692[91]				
uE_3	0.0695	-0.1741	-0.3666	0.3712	-0.0056[91]	-0.1093			
Total hCG	0.0466	0.6912	0.4598	-0.2295		0.1920	-0.3808		
Free β-hCG	0.1471	0.5735	0.7797	-0.3004	-0.3058[91]	0.1981	-0.4356[58]	0.8178	
Inhibin-A	0.1854	0.2493	0.2909	-0.1842	-0.0053[91]	0.1770	-0.3276	0.4197	0.4384

Appendix K Statistical parameters: Neural tube defects

Mean maternal serum AFP levels (log_{10} MoM) in singleton pregnancies with neural tube defects according to gestational age

Pregnancy†	Mean
Anencephaly [76]	
15 weeks	0.6412
16	0.7469
17	0.8110
18	0.8335
19	0.8144
20	0.7537
21	0.6514
22	0.5075
Open spina bifida‡[76]	
15 weeks	0.4554 (0.6107)
16	0.5522 (0.7075)
17	0.6024 (0.7578)
18	0.6060 (0.7613)
19	0.5630 (0.7183)
20	0.4734 (0.6287)
21	0.3372 (0.4925)
22	0.1544 (0.3097)
Closed spina bifida [13]	0.0000 (0.1553)

† Unaffected mean set to 0

‡ Values in parentheses based on gestation estimated from biparietal diameter (BPD) measurement

Standard deviation of AFP (log_{10} MoM) in unaffected pregnancies and pregnancies with neural tube defects

Pregnancy	Standard deviation [41]			
	Gestational age estimated by			
	Dates		Scan	
	Without weight adjustment	With weight adjustment	Without weight adjustment	With weight adjustment
Unaffected	0.1688	0.1649	0.1579	0.1468
Anencephaly (Note 4&5)	0.3335	0.3316	n/a	n/a
Open spina bifida	0.3378	0.3358	0.3324	0.3272
Closed spina bifida	0.1688	0.1649	0.1579	0.1468

Mean maternal serum AFP level (log_{10} MoM) in unaffected twin pregnancies and twin pregnancies with neural tube defects

Pregnancy	Mean [10]	
	Gestational age estimated by	
	Other than BPD	BPD
Unaffected	0.3284 [11]	0.3284 [11]
Anencephaly (Note 4 & 5)	0.8749	n/a
Open spina bifida	0.6435	0.7212 (see note 6)
Closed spina bifida	0.3284	0.4060 (see note 6)

Correlation coefficients of AFP (log_{10} MoM) between first and repeat tests in unaffected pregnancies and pregnancies with neural tube defects

Pregnancy	Correlation coefficient [44]			
	Gestational age estimated by			
	Dates		Scan	
	Without weight adjustment	With weight adjustment	Without weight adjustment	With weight adjustment
Unaffected	0.7698	0.7345	0.7487	0.6727
Anencephaly (Note 4&5)	0.9394	0.9301	n/a	n/a
Open spina bifida	0.9407	0.9331	0.9339	0.9254
Closed spina bifida	0.7698	0.7345	0.7487	0.6727

n/a Not applicable

Notes:

1. When calculating the NTD risk estimate the truncation limits applied to the AFP MoM value are 1.0 to 5.0[78]

2. The birth prevalence of neural tube defects in twin pregnancies is taken to be 2.28 times the prevalence in singleton pregnancies. [73]

3. The open spina bifida prevalence is taken to be 0.84 times that of spina bifida.[5]

4. When a BPD measurement is supplied, anencephaly is excluded and the NTD risk is given for spina bifida alone.

5. When calculating the anencephaly risk and a scan measurement other than BPD is supplied, the statistical parameters for gestational age estimated by dates are used (N J Wald, personal communication).

6. The mean AFP values in spina-bifida twin pregnancies with GA estimated from BPD are derived from the non-BPD means by assuming that:

i) Only one fetus in affected twin pregnancies is affected

ii) In expectation, the GA estimated is based on the means of the two BPDs

iii) AFP levels in spina bifida fetuses where gestation is measured by BPD are 43% higher[79]

7. In women with insulin-dependent diabetes mellitus, the prevalence of both anencephaly and spina bifida is taken as 5 per 1000 [90]

Appendix L Statistical parameters: Trisomy 18

Means, standard deviations and correlation coefficients (log_{10} MoM) for unaffected and trisomy 18 pregnancies, and truncation limits (MoM), for serum markers and nuchal translucency (NT)

Marker†		Unaffected pregnancies	Trisomy 18 pregnancies
MEAN*			
2nd trimester [18]	AFP		-0.1871
	uE_3		-0.3665
	hCG		-0.4437
	free ß hCG		-0.4252
1st trimester [66]	hCG		-0.4290
	free ß hCG		-0.6293
	PAPP-A		-0.5541
	NT		0.2977
STANDARD DEVIATION			
2nd trimester	AFP [42]	0.1688	0.1980
	uE_3 [18]	0.1391	0.2938
	hCG [18]	0.2401	0.3772
	free ß hCG [18]	0.2508	0.4302
1st trimester [66]	hCG	0.2127	0.3259
	free ß hCG	0.2978	0.3142
	PAPP-A	0.3127	0.2309
	NT	0.1325	0.2943
CORRELATION COEFFICIENTS‡			
2nd trimester	AFP,uE_3 [42]	0.2459	0.2466
	AFP,hCG [42]	0.0859	0.0612
	AFP, free ß hCG [42]	0.0843	0.1644
	uE_3,hCG	-0.2122 [19]	0.0944 [18]
	uE_3, free ß hCG [18]	-0.1770	-0.1770
1st trimester	free ß hCG, PAPP-A [66]	-0.004	0.420
	NT, free ß hCG [36]	-0.0570	0.4164
	NT, PAPP-A [36]	0.0000	0.0927
	hCG, PAPP-A [66]	0.0050	0.4490

		All pregnancies
TRUNCATION LIMITS		
2nd trimester	AFP [19]	0.33 – 2.0
	uE_3 [19]	0.4 – 1.5
	hCG [19]	0.2 – 2.5
	free ß hCG[18]	0.2 – 2.5
1st trimester[66]	hCG	0.3 – 1.0
	free ß hCG	0.2– 1.0
	PAPP-A	0.2 – 0.7
	NT	0.8 – 2.2

† First trimester markers measured between 10 and 13 weeks of pregnancy, second trimester between 14 and 22 weeks

* Unaffected means for all markers set to 0

Birth prevalence of trisomy 18 is taken to be one tenth of the age-specific prevalence of Down's syndrome [19]

Appendix M Statistical Parameters: Trisomy 13

Means, standard deviations and correlation coefficients (log_{10} MoM) for unaffected and trisomy 13 pregnancies, and truncation limits (MoM), for serum markers and nuchal translucency (NT)

Marker†		Unaffected pregnancies[49]	Trisomy 13 pregnancies[82]
MEAN *			
2nd trimester	Inhibin	0.0000	0.2068
1st trimester	Free β-hCG	0.0000	-0.3279
	PAPP-A	0.0000	-0.5850
	NT	0.0000	0.3263
STANDARD DEVIATION			
2nd trimester	Inhibin	0.2078	0.2714
1st trimester	Free β-hCG	0.2651	0.2743
	PAPP-A	0.2495	0.1986
	NT (10 weeks)	0.1550 [75]	0.3014
	NT (11 weeks)	0.1275 [75]	0.3014
	NT (12-13 weeks)	0.1105 [75]	0.3014

CORRELATION COEFFICIENTS (UNAFFECTED PREGNANCIES) [49]

	First trimester				
	NT (10 weeks)	NT (11 weeks)	NT (12-13 weeks)	Free β-hCG	PAPP-A
First Trimester					
Free β-hCG	-0.0325	-0.0391	-0.0423		
PAPP-A	-0.0429	-0.0516	-0.0559	0.1395	
Second trimester					
Inhibin	-0.0415	-0.0499	-0.0540	0.2937	0.0237

CORRELATION COEFFICIENTS (AFFECTED PREGNANCIES) [82]

	NT	Free β-hCG	PAPP-A
First Trimester			
Free β-hCG	-0.1541		
PAPP-A	-0.1418	0.1476	
Second trimester			
Inhibin	0	0	0

		All pregnancies[82]
TRUNCATION LIMITS		
2nd trimester	Inhibin	0.5 – 2.0
1st trimester	Free β-hCG	0.3 -1.35
	PAPP-A	0.2 – 0.5
	NT	0.9 – 2.5

The age-specific live birth prevalence of trisomy 13 is given by [83]:

$$prevalence = \frac{1}{1+e^{9.53-3.25/\left(1+e^{-0.332(age-37.5)}\right)}}$$

The risk of an individual woman having a pregnancy affected with trisomy 13:

$$risk = \frac{1}{1+e^{9.53-3.25/\left(1+e^{-0.332(age-38.0)}\right)}}$$

Fetal Loss Rates

The fetal loss rates for tests carried out in the first trimester (12 weeks gestation) and second trimester (18 weeks gestation) are taken to be 49% and 42% respectively. [84]

Appendix N Statistical parameters: Smith-Lemli-Optitz syndrome (SLOS)

Means, standard deviations and correlation coefficients (log10 MoM) for unaffected and SLOS pregnancies, and truncation limits (MoM), for each serum marker

Serum marker†	Unaffected pregnancies ‡	SLOS pregnancies [47]
MEAN *		
AFP		-0.1427
uE_3		-0.6778
hCG		-0.1192
STANDARD DEVIATION		
AFP	0.1527	0.1465
uE_3	0.1351	0.3501
hCG	0.2260	0.3159
CORRELATION COEFFICIENTS		
AFP, uE_3	0.3140	0.3760
AFP, hCG	0.0950	0.2230
uE_3, hCG	-0.2150	0.3960
	All pregnancies	
TRUNCATION LIMITS [47]		
AFP	0.4 – 2.0	
uE_3	0.3 – 1.0	
hCG	0.3 – 1.5	

† All measured between 14 and 22 weeks of pregnancy

‡ Personal communication July 2001 from Foundation for Blood Research

* Unaffected means for all markers set to 0

The birth prevalence of SLOS is taken to be 1 in 20,000 [47]

Appendix O Statistical parameters: Pre-eclampsia

Means, standard deviations and correlation coefficients (log10 MoM) for unaffected and pre-elampsia pregnancies and truncation limits for serum markers[89]

Marker		Unaffected pregnancies	Pre-eclampsia pregnancies
MEAN			
1st trimester	PAPP-A	0.000	-0.0915†
	PlGF	0.000	-0.1079†
	MAP	0.000	0.0294†
2nd trimester	AFP	0.000	0.022
	uE_3	0.000	-0.060
	total hCG	0.000	0.060
	Free ßhCG	0.000	0.063
	inhibin-A	0.000	0.139
	PlGF	0.000	-0.174
STANDARD DEVIATION			
1st trimester	PAPP-A	0.2345	0.2540†
	PlGF	0.1611	0.1654†
	MAP	0.0353	0.0369†
2nd trimester	AFP	0.155	0.174
	uE_3	0.112	0.125
	total hCG	0.238	0.275
	Free ßhCG	0.282	0.318
	inhibin-A	0.188	0.265
	PlGF	0.210	0.286
		All pregnancies	
TRUNCATION LIMITS			
1st trimester	PAPP-A	0.20 to 3.00[88]	
	PlGF	0.40 to 2.50[88]	
	MAP	0.90 to 1.20[88]	
2nd trimester	AFP	0.82 to 2.50	
	uE_3	0.50 to 1.76	
	hCG	0.66 to 3.00	
	free ß hCG	0.59 to 3.00	
	inhibin-A	0.72 to 3.00	
	PlGF	0.30 to 1.40	

† Derived from reference [93]

CORRELATION COEFFICIENTS

	First trimester			Second trimester[89]					
Parameter	PAPP-A	PlGF	MAP‡	AFP	uE_3	Total hCG	Free β-hCG	Inhibin-A	PlGF
Unaffected									
First trimester[94]									
PAPP-A	1								
PlGF	0.3009	1							
MAP	-0.007	-0.0346	1						
Second trimester									
AFP	0.1160[88]	-0.1477[88]	0	1					
uE_3	0.1213[88]	-0.0547[88]	0	0.275	1				
Total hCG	0.0624[88]	-0.0854‡‡	0	0.197	-0.096	1			
Free β-hCG	0.0627[88]	-0.0854[88]	0	0.184	-0.096	0.85	1		
Inhibin-A	0.0237[88]	-0.1509[88]	0	0.074	0.023	0.343	0.356	1	
PlGF	0.3223[88]	0.4643[88]	0	0.302	0.102	0.165	0.177	0.144	1
Pre-eclampsia									
First trimester[94]									
PAPP-A	1								
PlGF	0.3544	1							
MAP	0.0355	0.0129	1						
Second trimester									
AFP	0.1160*	-0.1477*	0	1					
uE_3	0.1213*	-0.0547*	0	-0.222	1				
Total hCG	0.0624*	-0.0854*	0	0.306	-0.279	1			
Free β-hCG	0.0627*	-0.0854*	0	0.362	-0.308	0.939	1		
Inhibin-A	0.0237*	-0.1509*	0	0.353	-0.438	0.519	0.453	1	
PlGF	0.3223*	0.4643*	0	-0.149	0.343	-0.214	-0.187	-0.443	1

‡ Correlations assumed to be zero
‡‡ Correlation between PlGF and total hCG assumed to be the same as for PlGF and free ßhCG
* Correlations assumed to be the same as for unaffected pregnancies

The likelihood ratio obtained from the maternal serum markers is multiplied by either the likelihood ratio for when a previous pregnancy has or has not been affected with pre-eclampsia: **

Likelihood ratio when a previous pregnancy has been affected with pre-eclampsia $= \frac{7(1-p)}{(2+11p)}$

Likelihood ratio when a previous pregnancy has not been affected with pre-eclampsia or is a first pregnancy

$$= \frac{(p-1)(51p+8)}{(3p-2)(35p+4)}$$

where p is the prevalence.

** Jon Bestwick, personal communication

Appendix P Factors used for adjusting MoM values

Serum marker levels differ, on average, between twin and singleton pregnancies, and some differ between women with and without insulin-dependent diabetes mellitus, between smokers and non-smokers, and between women who undergo *in-vitro* fertilisation (IVF) and those who conceive naturally. This can lead to differences in the false-positive rate among the different groups screened at a fixed risk cut-off. For example, the screen-positive rate among IVF pregnancies screened with the **Quadruple Test** is about twice that in naturally conceived pregnancies for a risk cut-off of 1/300.[39] To avoid this, **αlpha** adjusts MoM values in twin, diabetic and IVF pregnancies, and in women who smoke, using the adjustment factors given in the table below. Since women with insulin dependent diabetes mellitus tend to be heavier than those without this condition, two adjustment factors are given, one used when a diabetic woman's MoM values are weight adjusted, and the other when they are not.

There are too few data in which two or more of these circumstances (twin, diabetic,IVF pregnancies, and women who smoke) apply in the same pregnancy. In these cases an adjustment factor can be derived by multiplying the adjustments factors for each circumstance. For example, the adjustment factor for uE3 for a woman who smokes and is diabetic (adjusted for weight) is 0.96 X 0.95 = 0.912. Other factors are derived in a similar way. This is the approach used in **αlpha.**

The table below also indicates by a superscript letter when the adjustment factor value was first used in **αlpha**. If there is no indication, the adjustment factor has always been used in the Windows version of **αlpha.**

Median marker levels (MoM) in twin, diabetic and IVF pregnancies and in smokers, relative to singleton, non-diabetic, and non-IVF pregnancies and non-smokers

Serum marker	Twin pregnancies †	Diabetic pregnancies †		IVF pregnancies	Smokers †
		Adjusted for weight	Not adjusted for weight		
Second trimester (14-22 weeks)					
AFP	2.13 [11]	0.88 [60, b]	0.77 [2]	n/a	1.05 [45,c]
uE_3	1.67 [11]	0.95 [60, b]	0.92 [14]	0.94 [39‡]	0.96 [45,c]
total hCG	1.84 [11]	n/a	n/a	1.14 [39‡]	0.77 [29,c,d]
free ß hCG	1.90 [15]	n/a	n/a	1.14 [39‡]	0.80 [45,c]
inhibin-A	1.99 [25]	n/a	n/a	n/a	see note (e)
First trimester (10-13 weeks)					
PAPP-A	1.86 [43]	n/a	n/a	0.91 [71, a]	0.81 [69, c]
free ß hCG	2.10 [43]	n/a	n/a	n/a	0.94 [69, c]
total hCG	1.87 [71, a]	n/a	n/a	n/a	0.80 [71, a]

† **αlpha** adjusts MoM values in a twin, diabetic and IVF pregnancies (see ‡) or in a smoker by dividing by the corresponding value in the table

‡ **αlpha** adjusts uE3, total hCG and free ß hCG MoM values in an IVF pregnancy by multiplying by the reciprocal of the corresponding value in the table, rounded to 1 decimal place (1.1, 0.9, 0.9 for uE_3, total hCG and free ß hCG respectively)

n/a No adjustment made

a) These adjustment factors were introduced in **αlpha** version 7.0V.

b) Prior to **αlpha** version 6.4AB the following adjustment factors were used for diabetic pregnancies:

Serum marker	Diabetic pregnancies	
	Adjusted for weight	Not adjusted for weight
Second trimester (14-22 weeks)		
AFP	0.82 [24]	0.77 [2]
uE_3	0.94 [24]	0.92 [14]
total hCG	n/a	n/a
inhibin-A	0.91 [24]	0.88 [24]
First trimester (10-13 weeks)		
PAPP-A	n/a	n/a
total hCG	n/a	n/a

c) The smoking adjustment factors are used from **αlpha** version 7.0P for users who upgraded from the DOS to the Windows version of **αlpha**. These factors replace any smoking factors specified by the users in the DOS versions of **αlpha**. For users who have only used the Windows version of **αlpha**, these factors have always been used.

d) Prior to version 7.1Q was 0.82.

e) The inhibin-A smoking adjustment factor is[97] :

$$Adjustment\ factor = 10^{(-1.016836+0.0169631 \times GA - 0.0000575 \times GA^2)}$$

The smoking adjusted MoM is calculated from :

$$Smoking\ adjusted\ inhibin - A\ MoM = \frac{Smoking\ unadjusted\ inhibin - A\ MoM}{Adjustment\ factor\ rounded\ to\ two\ decimal\ places}$$

For gestational ages of 21 weeks and 1 day and higher the adjustment factor is fixed equal to 1.71.

Prior to version 8.0.14120.22 was the smoking adjustment factor for inhibin-A was 1.62 [45,c]

Appendix Q Suggested factors for adjusting MoM values for differences between ethnic groups

Levels of the serum screening markers may differ, on average, in women of different ethnic groups. Also, average maternal weight may differ between ethnic groups.[23], **αlpha** provides two methods for allowing for such differences, the 'direct' method and the 'adjustment' method. For further information on selecting the appropriate method for your screening service, *see Section 5.13.6.*

If you choose the adjustment method, you need to specify adjustment factors that are used to correct for differences between the majority ethnic group and other groups. The adjustment factors may be derived from your own screening data or from the scientific literature. The table below provides published adjustment factors that could be used to allow for differences in four second trimester serum markers in black and South Asian women compared with Caucasian women.

Factors for adjusting for differences in serum marker levels and maternal weight in black and South Asian women compared to Caucasian women [96]

Ethnic Group	Serum Marker	Adjustment for differences in marker levels	Adjustment for differences in maternal weight
Black women	1st trimester		
	Free ß-hCG	1.06	1.05
	PAPP-A	1.55	1.11
	2nd trimester		
	AFP	1.10	1.05
	uE3	0.96	1.02
	Total hCG	1.15	1.03
	Free ß-hCG	1.07	1.05
	Inhibin-A	0.95	1.03
South Asian women	1st trimester		
	Free ß-hCG	0.95	0.94
	PAPP-A	1.14	0.89
	2nd trimester		
	AFP	1.01	0.94
	uE3	1.14	0.97
	Total hCG	1.12	0.95
	Free ß-hCG	0.99	0.94
	Inhibin-A	1.11	0.95
Oriental women	1st trimester		
	Free ß-hCG	1.17	0.91
	PAPP-A	1.31	0.82
	2nd trimester		
	AFP	1.10	0.92
	uE3	1.16	0.96
	Total hCG	1.30	0.91
	Free ß-hCG	1.23	0.89
	Inhibin-A	1.14	0.94

Appendix R Operating environment

Operating System

αlpha runs under the Windows® XP service pack 3, Windows® 7 (recommended) or Windows® 8 (recommended) operating systems. Microsoft .NET framework 4 is required. We recommend you configure your PC to download all the latest updates from Microsoft when these are available.

Database

The **αlpha** database is stored in Microsoft® SQL Server® (SQL Server® 2005, SQL Server® 2008 or SQL Server® 2012). In a single user configuration Microsoft® SQL Server® must be installed on the user's PC or on a server accessible to the PC. In a multi-user configuration SQL Server® must be installed on a server accessible to the client PC.

Hardware

You should ensure that your computers have the minimum hardware specification recommend by Microsoft ® for the operating system and/or version of SQL Server® you are using. **αlpha** should run satisfactorily on a computer with this minimum specification. A USB port and CD-ROM drive are required.

Single user configuration

In a single-user (standalone) configuration all **αlpha** program files reside in a single folder on your computer's hard disk (usually C:\Program Files\Logical Medical Systems Ltd\Alpha). **αlpha** files must not be placed in the root (C:\) folder.

αlpha database files normally reside in the default folder specified by SQL Server®.

You can also store your **αlpha** files on another drive or on a network server, if you prefer.

Multi-user Configuration

αlpha can be used in a multi-user (network) configuration on most computer networks (eg Novell Netware, Windows networks).

To use **αlpha** in a multi-user configuration all the **αlpha** files must be placed in a shared folder on a file server. You should consult your network administrator and your **αlpha** distributor before attempting to set up **αlpha** in a multi-user configuration.

Each **αlpha** workstation will require:

i) the ability to read, write, create and delete files in the **αlpha** folder on the server

ii) a separate licensed dongle (security key)

αlpha database files normally reside in the default folder specified by SQL Server®. Your database administrator should ensure that all **αlpha** users have SQL Server Security database roles db_datareader and db_datawriter on the SQL Server database used by **αlpha** . Please consult your network administrator for further information.

Display Screen

αlpha will work satisfactorily with most display screens; however, we recommend a display with a diagonal size of at least 19 inches (48.25 cm) and a resolution of at least 1280 x 1024 pixels. To avoid eye strain, ensure that you adjust the brightness and contrast settings of your screen to a comfortable level, that the lighting in your work area is suitably adjusted to avoid screen reflection, and that you take regular breaks during long periods of work at your computer.

Backups

You should make frequent backups of **αlpha** and the SQL server database used by **αlpha**.

Appendix S Advances in αlpha

Scientific advances:

αlpha 8 can be used for Down's syndrome screening using first trimester placental growth factor as a marker [88]. This marker was previously not available in αlpha.

αlpha 8 includes the latest statistical parameters for pre-eclampsia screening. Pre-eclampsia screening using first trimester PAPP-A, mean arterial pressure (MAP) and first and second trimester placental growth factor[89,93,94] is now possible. These markers were not previously available for pre-eclampsia screening.

αlpha 8 can calculate screening performance estimates for Down's syndrome, trisomy 18, SLOS, trisomy 13 and pre-eclampsia. Previously screening performance estimates for Down's syndrome only could be calculated. Since version 8.0.14120.22 the detection rate at a fixed false positive rate and the false positive rate for a fixed detection rate are both calculated.

αlpha 8 includes a gestation specific adjustment for inhibin-A for women who smoke.[97]. Prior to version 8.0.14120.22 the adjustment factor for inhibin-A was not gestation specific.

Technical advances:

αlpha 8 contains many advances which improve ease of use and user friendliness:

- Simpler navigation:
  - All features are grouped into one of three sections – **Patients, Statistics and Setup**
  - Easy to switch from one feature to another and back again. You can return to the first feature and carry on from exactly where you left it.
- Automonitor:
  - Provides an overview in a single screen of the performance of your screening program
  - Highlights issues which require further investigation
  - Complements the existing statistical and monitoring features in **αlpha**.
- Statistical analysis
  - Calculations up to 30 times faster.
  - Selection of date ranges for tabulation directly from graphs of median MoM values
- Live Screens:
  - Screens showing statistical results are updated immediately when the settings are changed.
- Latest computing technology
  - Uses Microsoft® SQL Server®, Windows® Presentation Foundation and .NET framework.