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Amniocentesis results: investigation of anxiety. The ARIA trial

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Abstract

Amniocentesis results: investigation of anxiety. The ARIA trial

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Objectives: The Amniocentesis Results: Investigation of Anxiety (ARIA) trial tested two hypotheses: first, that giving amniocentesis results out on a fixed date alters maternal anxiety during the waiting period, compared with a policy of telling parents that the result will be issued 'when available' (i.e. a variable date), and secondly, that issuing early results from a rapid molecular test alters maternal anxiety during the waiting period, compared with not receiving any results prior to the karyotype. The effects of the two interventions on anxiety 1 month after receiving karyotype results were also examined.
Design: A multi-centre, randomised, controlled, open fixed sample, 2 × 2 factorial design trial, with equal randomisation.
Setting: Twelve hospitals in England offering amniocentesis as a diagnostic test for Down's syndrome.
Participants: A total of 226 women who had had an amniocentesis were randomised between June 2002 and July 2004. Eight women with abnormal results or test failure were excluded post-randomisation.
Interventions: Issuing karyotype results on a prespecified fixed date, rather than issuing them as soon as they became available and issuing karyotype results alone, or subsequent to issuing results from a rapid molecular test for the most common chromosomal abnormalities.
Main outcome measures: Average anxiety during the waiting period, calculated using daily scores from the short version of the Spielberger State–Trait Anxiety Inventory (STAI). Recalled anxiety, measured 1 month after receiving karyotype results, using a rating scale. Anxiety at the 1-month follow-up, measured using the short-form STAI.
Results: There was no evidence that giving out karyotype results on a fixed or on a variable date altered maternal anxiety during the waiting period. However, the analysis only had sufficient power to detect a moderate to large effect. Issuing early results from a partial, but rapid, test reduced maternal anxiety during the waiting period, compared with receiving only the full karyotype results. This was a moderate to large effect. In addition, group differences in recalled anxiety reflected fairly closely the differences in anxiety women had experienced while waiting for results. One month after receiving normal karyotype results, anxiety was low in all groups, but women who had been given rapid test results were more anxious than those who had not. This was a small to moderate effect.
Conclusions: Since there are no clear advantages in anxiety terms of issuing karyotype results as soon as they become available, or on a fixed date, women could be given a choice between them. Rapid testing was a beneficial addition to karyotyping, at least in the short term. This does not necessarily imply that early results would be preferred to comprehensive ones if women had to choose between them. There should be further research, including more qualitative studies, into the causes, characteristics and consequences of anxiety associated with prenatal testing. The effects of different testing regimes on short- and long-term anxiety, on the preferences of women and on the relationship between anxiety and preference should be investigated. More research is needed on the ways in which information might be used to minimise anxiety in different testing regimes. Further research is also required into the policy implications of incorporating individual preferences for different testing regimes into prenatal testing programmes.

Contents

List of abbreviations

ARIA	Amniocentesis Results: Investigation of Anxiety
CI	confidence interval
CTRU	Clinical Trials Research Unit
CVS	chorionic villus sampling
FISH	fluorescence *in situ* hybridisation
HAQ	Health Anxiety Questionnaire
IAC	Independent Analysis Committee
ITT	intention-to-treat
LREC	Local Research Ethics Committee
MRC	Medical Research Council
MREC	Multi-centre Research Ethics Committee
PCR	polymerase chain reaction
PP	per-protocol
R&D	research and development
SAUC	standardised area under the curve
SD	standard deviation
SOS	Significant Others Scale
STAI	State–Trait Anxiety Inventory
TMG	Trial Management Group
TSC	Trial Steering Committee

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Many pregnant women experience anxiety while waiting for the results of diagnostic tests. Policies and practices intended to reduce this anxiety require evaluation.

Objectives

The Amniocentesis Results: Investigation of Anxiety (ARIA) trial tested two hypotheses:

- Giving amniocentesis results out on a fixed date alters maternal anxiety during the waiting period, compared with a policy of telling parents that the result will be issued 'when available' (i.e. variable date).
- Issuing early results from a rapid molecular test alters maternal anxiety during the waiting period, compared with not receiving any results prior to the karyotype.

The effects of the two interventions on anxiety 1 month after receiving karyotype results were also examined.

Design

A multi-centre, randomised, controlled, open fixed sample, 2×2 factorial design trial, with equal randomisation.

Setting

Twelve hospitals in England offering amniocentesis as a diagnostic test for Down's syndrome.

Participants

A total of 226 women who had had an amniocentesis were randomised between June 2002 and July 2004. Eight women with abnormal results or test failure were excluded post-randomisation.

Interventions

Two interventions were used in the trial:

- issuing karyotype results on a prespecified fixed date, rather than issuing them as soon as they became available
- issuing karyotype results alone, or subsequent to issuing results from a rapid molecular test for the most common chromosomal abnormalities.

Main outcome measures

Three outcome measures were considered:

- average anxiety during the waiting period, calculated using daily scores from the short version of the Spielberger State–Trait Anxiety Inventory (STAI)
- recalled anxiety, measured 1 month after receiving karyotype results, using a rating scale
- anxiety at the 1-month follow-up, measured using the short-form STAI.

Results

No evidence was found that giving out karyotype results on a fixed or on a variable date altered maternal anxiety during the waiting period. However, the analysis only had sufficient power to detect a moderate to large effect. Issuing early results from a partial but rapid test reduced maternal anxiety by a clinically significant amount during the waiting period, compared with receiving only the full karyotype results. This was a moderate to large effect.

Additionally, group differences in recalled anxiety reflected fairly closely the differences in anxiety that women had experienced while waiting for results. One month after receiving normal karyotype results, anxiety was low in all groups, but women who had been given rapid test results were more anxious than those who had not. This was a small to moderate effect.

Conclusions

Implications for healthcare

Since there are no clear advantages in anxiety terms of issuing karyotype results as soon as they become available, or on a fixed date, women could be given a choice between them.

Rapid testing was a beneficial addition to karyotyping, at least in the short term. This does not necessarily imply that early results would be preferred to comprehensive ones if women had to choose between them.

Recommendations for research

Further research could be considered for the following:

- more qualitative studies into the causes, characteristics and consequences of anxiety associated with prenatal testing
- the effects of different testing regimes on short and longer-term anxiety, on the preferences of women, and on the relationship between anxiety and preference
- consideration of the ways in which information might be used to minimise anxiety in different testing regimes
- policy implications of incorporating individual preferences for different testing regimes into prenatal testing programmes.

Chapter 1
Introduction

Health service users may wait days or weeks for important test results such as karyotyping by standard culture following amniocentesis, on which decisions about a wanted pregnancy may hinge. Unsurprisingly, many parents experience high anxiety[1–6] or even anger and guilt[7,8] while waiting.

In November 1999, the HTA programme issued a call for proposals addressing the topic: 'Minimising parental anxiety while waiting for, and receiving, results of antenatal tests'. Interventions targeting psychological and organisational factors, rather than the laboratory technologies themselves, seemed the most promising at that time. The study that was initially commissioned in response to that call sought to evaluate, using a factorial design, a psychological intervention in the form of a 'debriefing leaflet' and an organisational intervention relating to the predictability of 'results day'. However, before the project began, it became apparent that developments in laboratory technology that would threaten both the feasibility and the relevance of the planned study were being introduced into NHS practice and, further, that the psychological effects of the new technology were themselves unknown.

In consultation with the HTA, the aims of the study were changed: answering three questions was judged impractical, so the organisational intervention was retained, but – reluctantly – the debriefing leaflet was dropped and the effect on anxiety of adding a new molecular test to existing practice was substituted. The change of intervention necessitated a number of more detailed changes to the trial, including losing a qualitative component and modifying the primary end-point, but protocol changes were made before the project began. The properties of the new tests are outlined below, before a more general introduction to the topic of anxiety associated with prenatal testing and the rationale for the study conducted.

Developments such as chorionic villus sampling (CVS), cell culture directly on examination slides, fluorescence *in situ* hybridisation (FISH) and polymerase chain reaction (PCR), may reduce the waiting period and hence anxiety levels, but all have drawbacks. CVS has higher procedure-related miscarriage risks, direct slide culture is expensive and rapid molecular tests do not detect all important chromosome abnormalities.

Conventional karyotyping involves setting up cell cultures from the amniotic fluid sample obtained at amniocentesis. Only when these are established, a process that can take 2–4 weeks, are the cells prepared for full karyotype analysis. FISH and PCR analyses, in contrast, are performed on uncultured cells, with results typically available in 3–4 days. In the FISH procedure, cells are fixed with a cover-slip and stained with chromosome-specific DNA probes labelled with a fluorescent marker. With PCR, selected regions of the genome are amplified by the PCR and then quantified using fluorescent markers. Unlike the conventional test, where most structural chromosomal abnormalities can be diagnosed, FISH and PCR give results only for the specific regions of the genome that are tested. A typical approach is to test for the five most common structural chromosomal abnormalities among newborns, namely trisomy 21 (Down's syndrome), 18 (Edwards syndrome), 13 (Patau syndrome) and numerical X and Y abnormalities (i.e. the sex chromosomes).

In terms of the timing and comprehensiveness of the results, FISH and PCR may be considered equivalent, so for brevity the term 'Rapid test' is used here to refer to both.

In addition to taking longer, there is more variation in the timing of results from karyotyping. Most UK centres inform women of this variability, and tell them that their results will be communicated as soon as the test is complete, which generally takes between 14 and 21 days.

In our experience, amniocentesis anxiety occurs in three phases, each related to different concerns. Prior to the test, women worry whether to undergo it at all; immediately afterwards, they worry whether the test caused harm to the baby; and finally, as the result approaches, they worry about the outcome.

Anxiety about miscarriage probably occurs mainly in the first 11 days, since this is when doctors and women believe this occurs. Anxiety about

karyotype results is likely to increase in importance and in magnitude as time progresses. If the woman knows a Rapid test is being conducted, anxiety may become concentrated in the first 4 days, the maximum time that this result normally takes.

Anxiety surrounding the amniocentesis decision and the impact on anxiety of different diagnostic test results have been well researched, but relatively little is known about changes in anxiety over time while results are awaited[6] and even less about factors which might alter this anxiety. It seems likely that aspects of service delivery might influence the anxiety women experience during this period. National Screening Committee guidance, for example, states that test results should be issued as quickly as possible, and the practice of issuing karyotype results as soon as they become available is clearly in keeping with that policy. One of the obvious attractions of Rapid testing is that some information can be obtained and passed on to the woman in a few days rather than a few weeks.[9]

The present study was initially commissioned to look at the effect on anxiety of altering the methods for issuing karyotype results but, as described above, during the commissioning process, it became apparent that Rapid tests would soon be widely available, so the effect of incorporating this was also evaluated. For both of these interventions, 'common-sense' considerations would suggest that 'early is better'. Women who learn that their baby does not have Down's syndrome are spared several days' anxious waiting, and if the baby is affected, an earlier termination can be offered. However, there are psychological arguments to the contrary, explained below.

The experience of anxiety

Anxiety is a 'normal' emotional state experienced when something an individual values is threatened. Common anxiety-inducing situations include occasions when individuals believe their performance will be evaluated and situations concerning a person's health and well-being. Health-related anxiety ranges from relatively brief, minor episodes associated with a particular procedure, through persistent generalised concern or sensitivity to one's physical health,[10] to extremes of anxiety that are recognised as mental disorders.

Contemporary psychological thinking recognises that anxiety comprises several components.[11] **Cognitively** it is experienced as a feeling of apprehension. Accompanying this is a mixture of mental restlessness and agitation and recurrent thoughts about the source. Efforts to suppress the thoughts are usually only partially successful and the suppressed thoughts keep intruding into conscious experience. **Physical symptoms** are associated with arousal of the autonomic nervous system experienced as heightened physical tension, or 'being on edge'. **Behavioural** consequences include difficulty in maintaining an ongoing task.

A range of self-report anxiety scales have been developed. Some measure anxiety in general whereas others measure anxiety associated with specific threats, e.g. social evaluation or health. A second distinction is between measures that reflect a person's current state (state anxiety) or their habitual level of anxiety (trait anxiety). Whereas trait anxiety is regarded as relatively fixed and unmodifiable, state anxiety reflects the fluctuation of anxiety attributable to changes in the person's context and situation. The choice of scale depends on the research question. If the main focus is, as here, on the woman's daily experience, then a measure of state anxiety is appropriate. A measure of general anxiety is also desirable in a study of amniocentesis, as a woman is likely to be anxious about several different aspects of the experience.

Anxiety can also be measured at the time it is experienced or as it is recalled, and the two methods may differ.

Social and situational influences on anxiety

A woman's anxiety while waiting for amniocentesis results is likely to be influenced not just by aspects of the way in which services are delivered, but also by other psychological and social aspects of her life. Pregnancy and childbirth are inherently social, with partners and immediate family members advising and providing support. Social support is an established predictor of psychological well-being in many settings, and it is plausible that it helps alleviate anxiety in the prenatal testing context.

Issuing test results as soon as they become available

At one level, this is self-evidently good practice – so much so that it is included in policy documents and guidelines.[12] However, it may be counter-

productive, because it makes the timing of the result unpredictable. The degree to which a threat is predictable is a major influence on anxiety.[13–15] Knowledge of when and where a threatening event will occur generally confines the experience of anxiety to a smaller anticipatory 'window'. Under these circumstances, the peak magnitude of anxiety (normally experienced just prior to the event) may not be reduced, but the total anxiety experienced up to that point is truncated. Evidence from experimental studies indicates that, when offered a choice, individuals tend to choose predictable situations.[13–15] The implication for practice in issuing karyotype results would be to inform women that they would be given their result on a fixed day post-amniocentesis, e.g. day 18, thereby isolating the anticipatory window described above, and hence reducing anxiety overall.

Rapid testing

The introduction of Rapid testing would appear to provide an obvious solution to reducing the anxiety from diagnostic testing, by truncating the waiting period. However, the effect may not be straightforward.

In the diagnostic testing programme studied here, Rapid testing was followed by full karyotyping. If anxiety is essentially focused on Down's syndrome, then it should fall following a negative Rapid test result, with little further fall after the full karyotype results. Another possibility is that Rapid testing will have a 'dose–response' effect, reducing anxiety in proportion to the information provided, so that after being given a negative result from a Rapid test a woman need only be concerned with the remaining (generally lower probability) disorders. In this formulation, Rapid testing lowers anxiety by reducing the probability of the perceived threat and this leads the woman to reappraise the magnitude of the threat.

Alternatively, Rapid testing may have counter-productive consequences if partial information has the effect of 'raising the stakes' by removing some – but not all – barriers to the desired end result, or if two rounds of results just prolong the period over which important information is awaited.

Finally, women may falsely perceive Rapid testing as providing a complete diagnostic test and in a small proportion of cases the woman will be falsely reassured that she is carrying a healthy foetus, only to be informed to the contrary when full karyotyping is available.

Measuring anxiety over time

Comparison of anxiety while waiting for results requires a method for summarising anxiety over a period of time. Alternative indicators might include peak, average or total anxiety over the period, with the latter two measures requiring some method of summation.

A temporal integration model states that the total amount of anxiety experienced in the period is summed, that is, an area under the curve. In the simplest version of this model, equal moments of time are given the same weight. In this model, women with shorter but more intense experiences of anxiety will recall their anxiety as the same as a woman with longer but less intense experience of anxiety. An alternative **weighted averaging** model can generate seemingly counter-intuitive predictions. This model stipulates that the moments of affective experience are averaged to form a global impression. Thus, having additional low-intensity moments (a longer experience of anxiety) will reduce the overall average and result in the recalled experience of less anxiety. It is also possible to refine the model by varying the weights used in averaging – as perhaps not all moments have equal psychological weight. Whereas the **temporal integration** model stipulates that recalled anxiety is a function of the duration and intensity of the experience, the **weighted averaging** model can be adjusted to modify the influence of the duration of the experience (by adjusting the weights of some moments). Redelmeier and Kahneman[16] have suggested that memory for affective experiences is subject to **duration neglect**, in which some moments of the experience are ignored and other ones privileged. They suggest that a **peak-end** rule best fits the data. Thus shorter intense episodes of anxiety may be recalled as more intense than longer experiences which reach the same peak but in which the end of the experience is a lower intensity. This model fits experimental data and 'real-world' data. Redelmeier and Kahneman[16] recorded in real time the intensity of pain experienced by patients undergoing colonoscopy and lithotripsy and then examined their retrospective evaluations of the total pain of the medical procedure. Patients' judgments of total pain was strongly correlated with the peak pain and with pain recorded during the last 3 minutes of the procedure. In a second study, patients undergoing colonoscopy were randomly assigned to have a short interval added to the end of their procedure during which the tip of the colonoscope

remained in the rectum for an additional 3 minutes (additional low-intensity pain). Patients who underwent the extended procedure rated the entire experience as less unpleasant although they experienced more pain in real time. Perhaps more importantly from a health case perspective they were more likely to return for a repeat colonoscopy (odds ratio = 1.41, $p = 0.038$) in subsequent years.

Rapid testing may be beneficial because it lowers the magnitude of anxiety at the end of the total period of waiting. According to the peak-end duration neglect model, this pattern of experience will bias recall in a beneficial manner. On the other hand, timing of the result of the Rapid testing is broadly coincidental with the risk period for spontaneous abortion occurring as a result of the procedure. It is not known whether the concurrence of two anxiety-inducing threats will enhance the woman's experienced anxiety. The experienced anxiety may therefore be of one intense peak that will subsequently increase the recalled anxiety.

Lasting effects on anxiety

In addition to the distinction between experienced and recalled anxiety, the possibility of enduring effects must also be considered. These were observed in the prenatal screening context by Marteau and colleagues more than 12 years ago,[17] and following a recent review of the available literature, Green and colleagues[6] concluded: "Anxiety in 'false' positives may … not return to normal levels; some residual anxiety may remain, possibly over extended periods of time." Some authors have suggested that this residual anxiety might be a result of conflicting messages from health professionals: the (screening) test result is 'probably nothing to worry about', whereas the offer of further (diagnostic) testing conveys just the opposite.[18] Others have observed the development of generalised feelings that 'something unexpected' might go wrong with the pregnancy,[19] and it has been argued that, once created, the feeling of 'being at risk' may be hard to dispel.[20] This effect may be similar to the 'vulnerable child syndrome', which has been observed in some parents following episodes of illness in their children.[20,21]

Studies of other diagnostic tests also suggest that the impact of clinical reassurance may have only a transient effect.[22]

Recent research and policy developments on Rapid testing

Rapid testing is a relatively new technology, and little information is available on the psychological impact of its use. Until recently, it has always been offered in addition to a testing programme based on karyotyping, in which situation any benefit could only be psychological, as the test neither provides extra information nor permits termination by a different method. There have been two comparative studies of the effect of such a policy addition on anxiety.

One small randomised trial ($n = 60$) from Hong Kong examined the effects on anxiety in women screen-positive for Down's syndrome of adding Rapid testing to a programme based on karyotyping.[23] Anxiety was measured [using the Speilberger State–Trait Anxiety Inventory (STAI),[24] which is a measure of general anxiety] at 3 days post-amniocentesis, when Rapid testing results were known in one group, and at 3 weeks, when standard karyotype results were known in both groups. Contrary to expectations, anxiety scores did not differ between the two groups at either time point, but did increase in both groups over time.

In the other study, anxiety data were collected (using the short form of the STAI) from two non-randomised groups of women who had had an amniocentesis.[25] One group ($n = 141$) were given Rapid test results and karyotype results and the other group ($n = 53$) just the karyotype results. Baseline anxiety was measured when women attended amniocentesis clinics, after test results by postal questionnaire sent with the results, and by an additional postal questionnaire 4 weeks after the karyotype result. The two groups were comparable at baseline, but subsequent statistical analyses were not based on between-group comparisons, but rather on changes within each group over time. The Rapid test group showed a fall in anxiety on receipt of their Rapid test results, a further fall on receipt of the full karyotype results, but no further fall at follow-up. The comparison group showed a fall when they received their full karyotype results, and a further fall at 4 week follow-up, at which point the two groups had very similar scores.

To summarise: in Hong Kong, anxiety rose over the results period, and no benefit was found from issuing Rapid test results, whereas in the UK, anxiety fell and there was some evidence of benefit from Rapid testing. Neither study looked at

anxiety in the days preceding karyotype results. In other observational studies,[26,27] more anxious women made different choices about additional tests, so the effects on anxiety of providing the additional test results could not be evaluated. The interpretation of results from an ongoing US study[28] of the effects of FISH on anxiety will be problematic for the same reason.

Aims

The present study was a randomised trial, designed to test the following hypotheses:

- That giving amniocentesis results out on a fixed date with an undertaking not to telephone earlier even if possible alters maternal anxiety during the waiting period, compared with a policy of telling parents that the result will be issued 'when available' (i.e. variable date).
- That the issuing of early results from a Rapid test analysis alters maternal anxiety during the waiting period, compared with not receiving any results prior to the karyotype.

The study used a diary methodology to collect the daily experience of anxiety in real time in order to minimise possible memory bias, and also to collect data on key psychological and social predictors of anxiety, in order to take this contextual information into account when examining the effects of the two service factors.

Chapter 2
Methods

Objectives

The objectives of the Amniocentesis Results: Investigation of Anxiety (ARIA) trial were to test the following hypotheses:

- That giving amniocentesis results out on a planned date (fixed date) with an undertaking not to telephone earlier, even if possible, alters maternal anxiety during the waiting period, compared with a policy of telling women that the result will be issued as soon as available (variable date).
- That the issuing of early results from a partial but rapid analysis (Rapid test) alters maternal anxiety during the waiting period, compared with receiving only the full karyotype analysis (no Rapid test).

Trial design

The trial was a multi-centre, randomised, controlled, open fixed sample, 2 × 2 factorial design trial, with equal randomisation, in women having an amniocentesis test. Women were randomised to receive a Rapid test or no Rapid test, and to be issued with results on a fixed date or on a variable date.

Trial centres

Initially centres in Yorkshire were invited to participate in the ARIA trial and this was subsequently extended to across the UK. Centre participation required six criteria to be met as follows:

1. Cytogenetics laboratory undertook a full karyotype using the karyotype test and a Rapid test of either FISH or PCR.
2. Rapid testing was not undertaken as 'standard' for all amniocentesis samples.
3. The trial was supported by the laboratory staff.
4. Privately funded Rapid testing was not offered routinely to those ineligible for an NHS-funded Rapid test in the research centre.
5. The trial was supported by the obstetrics medical staff in the research centre.
6. The trial was supported by the antenatal midwifery team/antenatal screening co-ordinator in the research centre.

Following set-up in the Yorkshire centres, a review of the cytogenetics laboratories across the UK was undertaken and where criteria 1–3 applied to the cytogenetics laboratories, Fetal Medicine and Obstetric Consultants in those regions were invited to participate by letter. Also, relevant Regional Ante-Natal Screening Coordinators were consulted about practice across the region and were asked to disseminate information about the trial to key midwives from the potential centres. Local antenatal screening practice was discussed with medical and midwifery staff from potential centres and it was established whether local policy would permit ARIA trial participation. Where local policy did not rule out participation, centres were asked whether they would support the trial.

At the outset, 25 UK cytogenetics laboratories were identified and nine met criteria 1 and 2. Of these, seven initially agreed to support the trial although three subsequently were unable to participate as Rapid testing became available for all amniocentesis samples. Of the clinical centres associated with the cytogenetic laboratories, 18 agreed to participate and 12 recruited women into the trial.

The study was conducted with the support of four laboratories, Yorkshire Regional Genetics Service, Merseyside Clinical Genetics Service, South Western Regional Genetics Service and Leicestershire Clinical Genetics Department, in 12 research centres:

1. Leeds General Infirmary
2. St James's University Hospital, Leeds
3. Bradford Royal Infirmary
4. Airedale General Hospital
5. Friarage Hospital, Northallerton
6. Pinderfields General Hospital
7. Castle Hill Hospital, Hull
8. York District Hospital
9. Liverpool Women's Hospital
10. Arrow Park Hospital, Warrington
11. Royal United Hospital, Bath
12. Leicester Royal Infirmary.

The remaining six centres (Harrogate, Hull, Pontefract, Halifax, Huddersfield and Nottingham) agreed to participate and obtained Local Research Ethics Committee (LREC) and research and development (R&D) approval, but were unable to recruit owing to organisational barriers (such as staff time), no eligible women available or a subsequent change in the local testing policy.

Eligibility

Pregnant women of $14^{+\ 0\ \text{days}}$ to $20^{+\ 6\ \text{days}}$ weeks' gestation, carrying a single foetus and undergoing amniocentesis, were included in the trial. Specific criteria for inclusion and exclusion were as follows.

Inclusion criteria

1. Woman was undergoing amniocentesis for the following primary indications:
   (a) Maternal age (women were included at any age provided that it was sufficient to make them wish for an amniocentesis).
   (b) Triple test risk sufficient to make the woman choose amniocentesis.
   (c) Single soft marker for Down's syndrome. This included the presence of abnormal nuchal translucency, a short femur or a dilated renal pelvis, provided that in combination with maternal age this was felt sufficient to indicate amniocentesis.
   (d) Parental anxiety.
2. Woman was able to read and complete the daily anxiety assessment.
3. Woman was aged at least 18 years.
4. Woman had given written informed consent (Appendix 2).

Exclusion criteria

1. Amniocentesis was performed primarily to diagnose a single gene disorder, neural tube defect or for rhesus disease.
2. The presence of a major structural abnormality was detected on ultrasound.
3. Either parent was carrying a balanced translocation.
4. The woman had previously entered the trial, that is, earlier pregnancy.
5. Insufficient amniotic fluid was collected (less than 12 ml).
6. A blood-stained sample of amniotic fluid was collected.
7. It was not possible to contact the woman by telephone at the appropriate time.

Post-randomisation exclusion

Women were excluded from the study post-randomisation if:

1. They received an abnormal result.
2. They experienced a miscarriage.
3. The karyotype test failed.

End-points

Primary end-point

Anxiety was measured using the six-item short form of the State Scale of the Spielberger STAI,[29] which is a measure of general anxiety, and recorded daily by the women from the day of amniocentesis to day 21. The primary end-point for both the fixed versus variable and Rapid test versus no Rapid test interventions was defined as the average anxiety during the waiting period. The waiting period for both interventions was defined as the period from amniocentesis day until the karyotype results day and was measured using the area under the curve standardised for the length of the waiting period [standardised area under the curve (SAUC)].

Secondary end-points

Secondary end-points using the six-item short form of STAI for the Rapid test versus no Rapid test intervention groups and fixed versus variable date intervention groups included the following measures:

- the peak anxiety in the waiting period, with the peak defined as the maximum anxiety score
- the length of time to the first peak anxiety
- the total anxiety in the 11 days following amniocentesis
- the average anxiety measured by the area under the curve standardised for the waiting period, from day 12 to karyotype results day
- the total anxiety from test day to day 21
- the total anxiety for the first 4 days following amniocentesis
- the total anxiety for the 7 days prior to karyotype results day
- anxiety measured 1 month after receiving the karyotype results.

Two further secondary end-points for both the Rapid test versus no Rapid test intervention groups and fixed versus variable date intervention groups using a 0 to 10 scale, where 0 represented not at all anxious and 10 represented very anxious, included:

- anxiety for the period around 10–12 days after they had had their amniocentesis test, recalled 1 month after receiving the karyotype results
- anxiety for the period 2–3 days just before they received their final karyotype result, recalled 1 month after receiving the karyotype results.

Recruitment and randomisation

Information about the study was given in one of two ways depending on the method of referral for amniocentesis. Women who had requested an amniocentesis were given both verbal and written information (Appendix 3) about the trial at the time the clinic visit for amniocentesis was arranged. It was expected that this would give most women at least a week to consider the trial.

Women who were having an amniocentesis due to a blood test result were likely to have very little time between the issuing of the blood test result and the clinic visit for amniocentesis. It was not considered ethical to overwhelm a woman in this position with the full trial information, but the trial was mentioned very briefly. The attending doctor or midwife arranging the amniocentesis would inform the woman that that there was a trial being carried out and mention that the woman may wish to allow some time following the amniocentesis to find out more about it. The information sheet was given to the woman at the amniocentesis clinic visit, when the attending doctor or midwife would further discuss the trial and establish whether the woman had further questions and if she was willing to take part. Where women indicated that they were interested in taking part, written informed consent was obtained.

After amniocentesis, women fulfilling the eligibility criteria and providing their fully informed written consent were randomised through an independent, central, secure 24-hour randomisation automated telephone service by the Clinical Trials Research Unit (CTRU), University of Leeds. Women were allocated to receive results on either a fixed date or a variable date. They were also randomised to either a Rapid test or no Rapid test. The randomisation was performed using minimisation (dynamic allocation using a prespecified computer-generated algorithm). The minimisation was stratified according to the woman's age (<35, ≥ 35 years) and most senior person present at the amniocentesis.

Interventions

Processing samples and issuing results

All samples were processed in each research centre's usual cytogenetics laboratory. For those samples allocated to Rapid test, the laboratory performed molecular analysis using FISH or PCR for chromosomes 21, 18, 13, X and Y. The laboratory performed a karyotype test to produce a full karyotype on all samples according to their usual protocol.

All Rapid test and full culture results for trial participants, whether normal or abnormal, were issued by the cytogenetics laboratories to the ARIA Research Midwife (or, in her absence, a midwife from the Leeds General Infirmary antenatal midwifery team) by fax. All normal results were issued by the ARIA Research Midwife, who contacted the women by telephone to issue results. The ARIA Research Midwife then confirmed with each centre that a normal result had been issued to the woman and sent the centre a copy of the result.

All abnormal results were immediately referred back to the responsible consultant. The ARIA Research Midwife liaised with them immediately upon receipt of the result and arrangements were made by the responsible consultant to issue the result as per local practice. All abnormal results were classified as post-randomisation exclusions and these women received no further contact from the ARIA team.

Rapid test versus no Rapid test

For participants randomised to receive a Rapid test, the interim partial result was expected to be available within 48 h. Women were told to expect the result of the rapid test within 3–4 days to allow for delays due to sample transportation/processing, weekends or bank holidays. The ARIA Research Midwife issued the rapid test as soon as available, following an agreed script (Appendix 4).

Participants randomised to undergo no Rapid test were told to expect a welcome call by the ARIA Research Midwife, 3–4 working days following the amniocentesis. The ARIA Research Midwife introduced herself and thanked the woman for participating in the trial, following an agreed script (Appendix 4).

Fixed date versus variable date

Participants were given the full culture result by the ARIA Research Midwife either as soon as available (variable date) or on day 18 (fixed date), depending on the randomised allocation.

Participants randomised to variable date were told that the ARIA Research Midwife would ring them with the result as soon as it was available, at any time from day 7 but usually between days 14 and 21 after the test.

Participants randomised to fixed date were told that 95% of results are available by day 18 and that they would be telephoned on that day. A convenient time was agreed, preferably morning or afternoon, but specific times including evenings and Saturdays were also arranged, reflecting practice in clinical centres issuing results on a fixed date. Participants in this group with an abnormal result were informed of this immediately irrespective of the 18-day plan. However, participants were not told that this would happen unless they asked the attending clinical team directly.

Assessments

Baseline assessments

The following information was collected for all eligible women who consented to trial participation, and was recorded by members of the attending clinical team:

1. eligibility checklist
2. name and date of birth
3. amniocentesis details
   (a) date of amniocentesis
   (a) gestation
   (c) name of person performing the amniocentesis
   (d) needle entry (number)
   (e) amniocentesis procedure problems
   (f) whether the woman asked when an abnormal result would be given
4. randomisation details
   (a) hospital number
   (b) consultant name
   (c) hospital name
   (d) date of informed consent
   (e) confirmation of eligibility
   (f) name and code of most senior staff present during amniocentesis
   (g) age <35 or ≥35 years
   (h) randomised allocation
5. contact details
   (a) agreed date and time for fixed date result (where applicable)
   (b) telephone contact details (including number and place of contact (e.g. home/work) for rapid test result (where applicable)
   (c) telephone contact details (including number and place of contact (e.g. home/work) for karyotype result (all women).

The following information was provided by all women who consented to trial participation and was recorded on self-completed forms prior to knowledge of the randomisation outcome. They were returned to the attending clinical team for posting to the CTRU:

1. Personal details and baseline characteristics
   (a) address
   (b) date of birth
   (c) GP details
   (d) reason for amniocentesis
   (e) demographics (lives with, marital status, ethnic origin)
   (f) education and employment
   (g) obstetric history
2. Baseline anxiety and support (prior to knowledge of randomisation outcome)
   (a) STAI[24]
   (b) Significant Others Scale[30] (SOS)
   (c) Health Anxiety Questionnaire[10] (HAQ).

The contents of the SOS and the HAQ are described in detail in the next chapter. These measures collect information on circumstances and attributes known to influence experienced anxiety.

Knowledge of the above baseline characteristics of participants was obtained in order to aid the interpretation of the trial results.

Follow-up assessments

The following information was provided by the women through a self-complete diary and postal questionnaires following knowledge of the randomised allocation, and were returned directly to the CTRU:

1. Daily diary up to day 21 (post-amniocentesis):
   (a) short version STAI[29]
2. 1 month after full culture result
   (a) short version of STAI[29]
   (b) recalled anxiety for the period around 10–12 days after the amniocentesis
   (c) recalled anxiety for the period 2–3 days just before the karyotype result.

The following information was recorded by the ARIA Research Midwife:

1. Rapid test results (if applicable)
   (a) test result (normal/abnormal/failed)
   (b) date result faxed by the laboratory

(c) date result telephoned to woman
(d) time result telephoned to woman
e. name of person who informed woman of the result

2. karyotype results
   (a) test result (normal/abnormal/failed)
   (b) date result faxed by the laboratory
   (c) date result telephoned to woman
   (d) time result telephoned to woman
   (e) whether woman telephoned at the date/time agreed and reason if not (where applicable)
   (f) name of person who informed woman of the result
3. post-randomisation exclusion/withdrawal
   (a) date excluded and reason
   (b) date withdrawn and reason.

In addition, serious adverse events (including miscarriage, hospital admission or other) were recorded by the ARIA Research Midwife or the attending clinical team.

Trial organisational structure

The Trial Steering Committee (TSC), which had an independent chair and four independent advisors (including a psychologist, obstetrician, statistician and consumer) (Appendix 5) was responsible for monitoring the conduct of the trial and safety according to the MRC Guidelines for Good Clinical Practice in Clinical Trials.

The Trial Management Group (TMG), led by Professor Jenny Hewison as Joint Chief Investigator (Appendix 6), was responsible for study design, protocol development, clinical set-up and clinical coordination, research centre training, ongoing management and monitoring, promotion of the study, analysis, interpretation and publication of the study.

Ethics and research approval

The study was submitted and approved by the North West Multi-centre Research Ethics Committee (MREC) and the LREC of each participating centre prior to entering women into the study. Agreement to undertake the trial was provided by each participating centre through the R&D approval processes.

The study was conducted in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, UK, October 2000. It was monitored by the TSC.

A member of the attending medical and midwifery team requested a woman's participation in the trial. Each woman was provided with a verbal explanation of the trial and a written explanation in the form of an information sheet (Appendix 3) and given the opportunity to ask questions. Written informed consent was obtained for all women prior to randomisation into the study (Appendix 2). The right of the woman to refuse consent without giving reasons was respected. Further, the women were free to withdraw from the study at any time, again without giving reasons and without prejudicing any further treatment or care.

Data quality and monitoring

Data management and monitoring were conducted to MRC (Medical Research Council) Guidelines for Good Clinical Practice in Clinical Trials and CTRU standard operating procedures. Data management practice included verification, database validation and 100% data checking following data entry. All missing and ambiguous data provided by the attending clinical team were chased until resolved. Data quality was assessed by the Senior Trial Coordinator and the ARIA Research Midwife.

The number of post-randomisation exclusions and women who withdrew from the trial were monitored throughout the recruitment period by the TMG and TSC. Compliance including number of diaries returned, number of diaries complete for the primary end-point and number of 1-month follow-up questionnaires returned were monitored throughout the trial by the Trial Statistician (blinded) and blinded by the TMG and TSC. The Trial Statistician identified that an unequal proportion of women randomised to no Rapid test and variable date did not return their diaries. This was reported to the TMG and a protocol amendment made so that women in the no Rapid test group received a welcome telephone call from the ARIA Research Midwife 3–4 days following the amniocentesis (Appendix 4).

Consent procedures

All consent forms were verified by the Senior Trial Coordinator on receipt and compliance reported to the TMG and TSC.

Safety
Adverse events were reported by the ARIA Research Midwife or the attending clinical team. Adverse events were reviewed by the ARIA Research Midwife. Blinded safety reports were reviewed by the TSC.

Statistical methods

Sample size
Since little was known about the difference in anxiety levels between women given fixed dates and variable dates to receive test results, and between women given a Rapid test or not, there were very few data available on which to base the sample size calculations. It was expected that 540 women could be recruited to the study over a period of 2 years. Assuming a drop-out/non-compliance rate of 10% and a 5% exclusion rate due to abnormal results, 462 women would have data available for analysis.

Cohen defined effect sizes of 0.2 SD as small, 0.5 as moderate, and 0.8 or greater as large.[32] Assuming that the score on the six-item short form of the State Scale of the Speilberger STAI[24] is normally distributed in the target population,[29] a sample size of 462 with 80% power at the 5% significance level would enable a moderate effect size of 0.26 standard deviation (SD) in the primary end-point to be detected.

The trial was closed at the end of the funded recruitment period with a sample size of 226 women. With this number of women the trial still had 80% power to detect a moderate effect size of 0.38 SD in the primary end-point, although this is a larger effect than that originally planned.

Interim analysis
A full interim analysis was not planned, although it was planned to assess the sample size assumptions after 12 months' recruitment (i.e. after recruitment of an estimated 270 women) and, if necessary, to increase the sample size. As the trial under-recruited, this was not carried out.

Unplanned interim analysis
However, an unplanned interim analysis for the Rapid test versus no Rapid test was carried out in order to prevent further delay to a policy decision and the desire to introduce Rapid testing for all women undergoing amniocentesis. At a meeting of the National Screening Committee held on 13 June 2003, it was agreed to defer a recommendation about Rapid testing until the trial results were available and these were expected in early 2004 (as per the original recruitment and analysis plan, Appendix 1). The general feeling of the antenatal screening committee was that Rapid testing has self-evident benefit and should be introduced for all women undergoing amniocentesis.

The TMG reported these difficulties to the TSC at the meeting of the TSC on 26 September 2003 and the committee discussed the issue of early analysis of the data. After full consideration of the expected recruitment figures, effect size scenarios and policy issues, the following recommendations were negotiated with Muir Gray (see below) and the NHS HTA Programme and undertaken:

- An Independent Analysis Committee (IAC) (Appendix 7) was established.
- The TSC and TMG remained blind to the results of the analysis (until the final trial database was locked), but discussed the issues surrounding the interim analysis with the IAC before the analysis took place and preprepared arguments and recommendations for each possible outcome following the analysis.
- An independent interim analysis was undertaken in February 2004 in order to inform the National Screening Committee for the Rapid test versus no Rapid test intervention.
- The IAC reported directly and in confidence to Professor Muir Gray, Programme Director of the National Screening Committee, and Professor Kent Woods, Director of the NHS HTA Programme.

Analysis populations
All summaries and analyses were planned using the intention-to-treat (ITT) population. The ITT population was defined as all women randomised who were not post-randomisation exclusions. Analysis was according to randomised group regardless of the intervention received.

The post-randomisation exclusions were predefined as women who received an abnormal result (either Rapid test or full culture result), had a failure of the full culture procedure or experienced a miscarriage during the waiting period.

A per-protocol (PP) population was also defined in the statistical analysis plan to exclude protocol violators and analyse according to intervention received if not as randomised. It was planned to review blinded data prior to analysis and only carry out PP analyses if there were a considerable

number of violators. A protocol violation was defined as a woman not getting the full culture result as randomised.

Analysis methods

All hypothesis testing was two-sided and at the 5% level. The ITT population was used for all analyses. The study was a 2×2 factorial design. Prior to analysis, tests were carried out to check if an interaction exists between the two main effects. Although this test has low power, there were no *a priori* reasons to expect an interaction between the interventions, therefore analysis would only be carried out as a four-group trial if there was evidence of an interaction based on this test.

Primary end-point

Average anxiety during the waiting period

Average anxiety during the waiting period was calculated using the daily scores from the short version of the STAI questionnaire. The total area under the curve was divided by the number of days in the waiting period to give the SAUC. The waiting period was defined as the number of days from amniocentesis test day to full culture results day inclusive.

A linear regression model was fitted using the SAUC outcome variable and adjusting for the treatment factors (fixed/variable, Rapid/no Rapid test). A further model also adjusted for stratification factors (age and most senior person present) and other covariates identified as being prognostic of outcome [reasons for having an amniocentesis (maternal age, triple test risk, single soft marker for Down's syndrome, parental anxiety) and previous problems (women who had had a previous miscarriage or a still birth/baby that died or a baby with a previous abnormality) and also gestation].

Missing data were assessed to check whether they occurred at random. Women with three or more consecutive days missing from the diary were excluded. Imputation, a technique for attributing a value to a missing data item, was used as follows. Diaries with one or two consecutive missing days had these scores imputed using linear interpolation. Those with a missing results day were imputed using the last observation carried forward provided that the previous day was available. This is thought to be a conservative imputation as women are expected to be more anxious on the day before results than on results day. Missing day 1 data were imputed as the average of their treatment group day 1 scores. This imputation was assessed using sensitivity analyses as described below.

Sensitivity analysis

Exclusion of protocol deviations

An analysis was carried out excluding variable date women who did not receive their results on the day they were available.

Imputation of day 1 scores

Analyses were carried out to test the robustness of the imputation used for the primary analysis as follows:

1. Excluding all women with day 1 data missing. This approach does not involve any imputation of data and reduces the sample size.
2. Defining the waiting period from day 2 to results day, that is, excluding all day 1 data. This approach does not involve excluding any women or imputation of data, but does lose potentially important data on anxiety on day 1.
3. Imputing lowest possible anxiety score for no Rapid test women and highest possible anxiety score for Rapid test women (and vice versa). This approach tests the robustness of the Rapid test versus no Rapid test results to having the average imputed.

Secondary end-points

Peak anxiety in the waiting period

The peak anxiety during the waiting period was calculated using the daily scores from the short version of the STAI questionnaire. The peak anxiety was defined as the maximum daily anxiety score during the waiting period. The waiting period was defined as the time from the amniocentesis test day to full culture results day. Linear regression was used to compare the peak anxiety between Rapid test versus no Rapid test women and between final results on a fixed versus variable date.

Length of time to the peak anxiety

The length of time to peak anxiety was measured in days, with the amniocentesis test day being the first day. If the peak anxiety score was recorded on more than one day, the peak was defined as the first day that the maximum score was recorded. If a woman did not complete her diary up to day 21, she was treated as censored on the last day she completed her diary. Cox regression was used to compare the time to the first peak between the Rapid test versus no Rapid test women and the fixed versus variable date women. Kaplan–Meier estimates were used to estimate median time to the first peak with 95% confidence intervals (CIs) for each treatment group.

Total anxiety in 11 days following amniocentesis
Total anxiety in the 11 days following amniocentesis was calculated using the summation of the daily scores from the short version of the STAI questionnaire from day 1 to day 11. The 95% CIs of the mean difference for each comparison were estimated, adjusted for each treatment factor. No formal statistical analyses were carried out.

Average anxiety from day 12 to karyotype results day
The SAUC was calculated using the daily scores from the short version of the STAI questionnaire from day 12 to the full culture results day inclusive. The 95% CIs of the mean difference for each comparison were estimated, adjusted for each treatment factor. No formal statistical analyses were carried out.

Total anxiety from test day to day 21
Total anxiety from test day to day 21 was calculated using the summation of the daily scores from the short version of the STAI questionnaire from amniocentesis test day (day 1) to day 21 inclusive. The 95% CIs of the mean difference for each comparison were estimated, adjusted for each treatment factor. No formal statistical analyses were carried out.

Total anxiety for the first 4 days
Total anxiety in the first 4 days following amniocentesis was calculated using the summation of the daily scores from the short version of the STAI questionnaire from day 1 to day 4, including the amniocentesis test day as the first day. The 95% CIs of the mean difference for each comparison were estimated, adjusted for each treatment factor. No formal statistical analyses were carried out.

Total anxiety for the 7 days prior to karyotype results day
Total anxiety in the 7 days prior to karyotype results day was calculated using the summation of the daily scores from the short version of the STAI questionnaire for the 7 days prior to the full culture result being issued, with results day as the last day. The 95% CIs of the mean difference for each comparison were estimated, adjusting for each treatment factor. No formal statistical analyses were carried out.

Recalled anxiety
One-month post-karyotype results women received a questionnaire regarding their recalled anxiety. This is measured on a 0–10 scale, with a higher number representing a higher level of anxiety. The questionnaire covered two time points: 10–12 days following amniocentesis test and 2–3 days immediately before karyotype results. The 95% CIs of the mean difference for each comparison were estimated, adjusting for each treatment factor. No formal statistical analyses were carried out.

Anxiety at 1-month follow-up
One-month post-karyotype results women were also asked to complete the short-form STAI on the day they completed the recalled anxiety questionnaire. Linear regression was used to compare the anxiety scores at 1-month follow-up between Rapid test versus no Rapid test women and between final results on a fixed versus variable date.

Chapter 3

Results

Introduction

This chapter presents the results of the trial, first looking at the sample size obtained, recruitment by centre, the analysis populations, the baseline data, including baseline quality of life questionnaires and a brief summary of the handling of missing data. A more detailed report is included in Appendix 8, and also data on the length of time to the karyotype results and the results of each of the end-points. The primary end-point analysis was adjusted for the intervention factors, the covariates that were regarded as important and finally by the baseline quality of life measurements.

Sample size

A total of 226 women were randomised between 24 June 2002 and 27 July 2004. Twelve centres randomised women into the trial. *Table 1* shows recruitment by centre.

Analysis populations

ITT

Table 2 shows the number of women randomised and the number of post-randomisation exclusions with reasons. Post-randomisation exclusions were predefined as an abnormal rapid or standard culture result, a loss of pregnancy or failure of karyotype. The ITT population consists of 218 women. All summaries and analyses are according to the randomised group.

PP

The PP population was not used for analysis owing to the low number of exclusions. Only five women were considered as major protocol violators and would therefore be excluded: one woman was ineligible as insufficient fluid had been collected, and this woman also withdrew from the study and changed to CVS. Two fixed-date women were given their results earlier than they had expected. One woman randomised to a variable date was given a fixed date in error and the result was issued on that fixed date. One fixed-date woman was given the incorrect date for day 18; it is unclear if this date was communicated to the woman, but she was telephoned on the correct day, possibly earlier than she expected.

Trial conduct

A CONSORT flow diagram of trial progress is presented in *Figure 1*.

Baseline characteristics

Table 3 summarises the reasons why women had the amniocentesis.

TABLE 1 *Recruitment by centre*

Centre	Rapid test	No Rapid test	Fixed date	Variable date	Total
Airedale General Hospital, Warrington	12	10	12	10	22
Arrow Park Hospital, Warrington	1	0	0	1	1
Bradford Royal Infirmary	11	5	6	10	16
Castle Hill Hospital, Hull	2	3	2	3	5
Friarage Hospital, Northallerton	10	9	10	9	19
Leeds General Infirmary, Leeds	28	34	34	28	62
Leicester Royal Infirmary	34	37	35	36	71
Liverpool Women's Hospital	5	8	6	7	13
Pinderfields General Hospital	0	1	0	1	1
Royal United Hospital, Bath	6	3	5	4	9
St James's University Hospital, Leeds	1	1	1	1	2
York District Hospital	2	3	3	2	5
Total	112	114	114	112	226

TABLE 2 *ITT population*

	Rapid test	No Rapid test	Fixed date	Variable date	Total
Randomised	112	114	114	112	226
Post-randomisation exclusions	5	3	2	6	8
Reasons:					
Abnormal karyotype result	1	3	1	3	4
Abnormal Rapid test	1	0	0	1	1
Karyotype result failures (1 sample was lost)	2	0	1	1	2
Ruptured membrane leading to a termination, treated as a miscarriage	1	0	0	1	1
Withdrawn					
Reasons:					
Abnormal scan	1	1	0	2	2
Procedure changed to CVS	1	0	0	1	1
ITT	107	111	112	106	218

Some women had more than one reason for having an amniocentesis. *Table 4* shows the number of reasons.

Women having more than one reason for having an amniocentesis are shown in *Table 5*. Thirteen women have given the two reasons of triple test and single soft marker for Down's syndrome.

The two women who had three reasons are both no Rapid test fixed-date women; their reasons were maternal age, single soft marker for Down's syndrome and parental anxiety.

Table 6 summarises the women's characteristics for the ITT population by the intervention factors. The baseline characteristics for the two intervention factors, Rapid versus no Rapid test and fixed versus variable date, are fairly well balanced across all the baseline characteristics.

Baseline quality of life questionnaires

Women had been asked to complete quality of life questionnaires at baseline, to assess their support networks from the significant others and their level of depression and/or anxiety. The data from these quality of life questionnaires are summarised in the tables below, and the primary end-point analysis has been adjusted for these scale scores to assess any difference between the factors.

Significant Others Scale (SOS)

Table 7 shows the proportion of women who completed each section of the SOS. More than 95% of women in each group completed the husband/partner section. Between 89 and 91% completed the mother section; this is fairly evenly distributed across the groups. Between 88% (variable date) and 95% (fixed date) completed the close friend section; this possibly indicates a difference between these two groups.

Table 8 shows the frequency of the number of sections that has been completed. The table shows that no-one completed all five sections of the SOS; approximately 60% completed three sections. A smaller proportion of Rapid test fixed-date women completed four sections than for the other groups, but a slightly larger proportion of these women have completed three sections than the other groups.

Tables 9–12 show the summary statistics of the actual and ideal emotional support and the actual and ideal practical support recorded at baseline, by intervention factor. The means and medians are very similar for all groups.

Tables 13 and *14* show the summary statistics for the discrepancy between the ideal and actual emotional and practical support by intervention factor. Again, the means and medians are very similar for all interventions.

Health Anxiety Questionnaire (HAQ)

The HAQ is made up of 21 questions that are scored from 1 to 4: 1 = not at all or rarely, 2 = sometimes, 3 = often, 4 = most of the time.

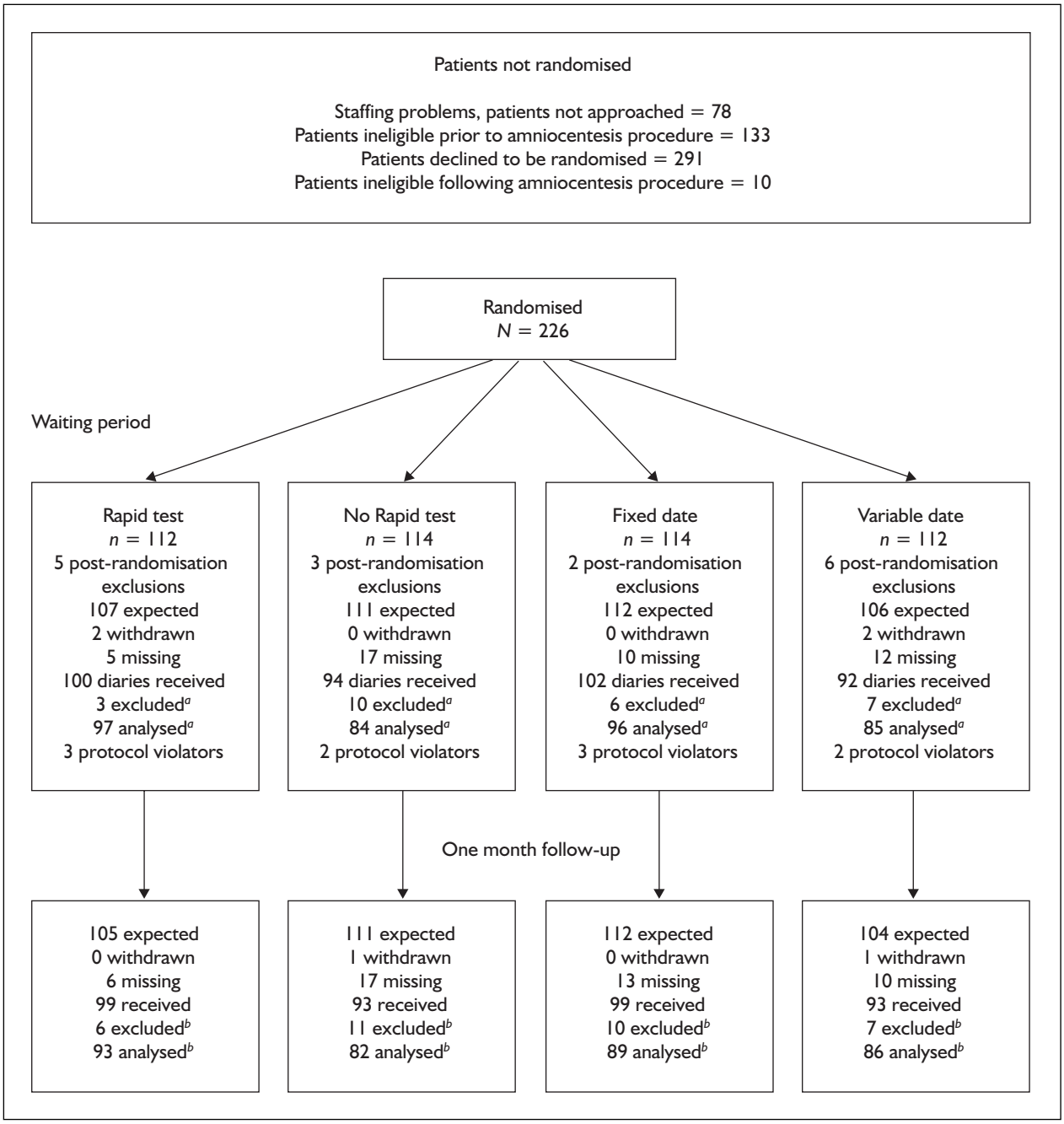

FIGURE 1 *CONSORT diagram.*
[a] *Women excluded from primary end-point analysis, insufficient evaluable data.*
[b] *Follow-up forms not received within the appropriate timeframe were not used in the analysis.*

TABLE 3 *Reasons why women had the amniocentesis*

Reason for amniocentesis	Rapid test *n* = 107	No Rapid test *n* = 111	Fixed date *n* = 112	Variable date *n* = 106
Maternal age	47 (44%)	43 (39%)	46 (41%)	44 (42%)
Triple test risk	65 (61%)	66 (60%)	63 (56%)	68 (64%)
Single soft marker for Down's syndrome	3 (3%)	9 (8%)	9 (8%)	3 (3%)
Parental anxiety	10 (9%)	11 (10%)	11 (10%)	10 (9%)
Total	125	129	129	125

TABLE 4 *Frequency of number of reasons for having an amniocentesis by intervention factor*

No. of reasons for amniocentesis	Rapid test *n* = 107	No Rapid test *n* = 111	Fixed date *n* = 112	Variable date *n* = 106
1	89 (83%)	95 (86%)	97 (86%)	87 (82%)
2	18 (17%)	14 (13%)	13 (12%)	19 (18%)
3	0 (0%)	2 (2%)	2 (2%)	0 (0%)

TABLE 5 *Women having more than one reason for an amniocentesis*

Reasons for amniocentesis	Rapid test	No Rapid test	Fixed date	Variable date	Total
Two reasons					
Maternal age and triple test	0	1	0	1	1
Maternal age and Down's syndrome	0	2	1	1	2
Maternal and parental anxiety	0	1	0	1	1
Triple test and Down's syndrome	8	5	5	8	13
Triple test and parental anxiety	2	2	3	1	4
Down's syndrome and parental anxiety	8	3	4	7	11
Three reasons					
Maternal age, Down's syndrome, parental anxiety	0	2	2	0	2
Total	18	16	15	19	34

TABLE 6 *Baseline characteristics by the two factor comparisons, Rapid versus no Rapid test and fixed versus variable karyotype result date*

	Rapid test *n* = 107	No Rapid test *n* = 111	Fixed date *n* = 112	Variable date *n* = 106
Age (years)				
Mean (SD)	35.8 (4.7)	35.9 (3.8)	35.8 (4.3)	35.8 (4.2)
Min., max.	18, 43	21, 43	21, 43	18, 43
Missing	1	0	0	1
Age (years)				
<35	36 (34%)	39 (35%)	38 (34%)	37 (35%)
≥ 35	71 (66%)	72 (65%)	74 (66%)	69 (65%)
Ethnic origin				
White	97 (91%)	106 (96%)	104 (93%)	99 (93%)
Black Caribbean	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Black African	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Indian	4 (4%)	3 (3%)	4 (4%)	3 (3%)
Asian	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Other	1 (1%)	2 (2%)	1 (1%)	2 (2%)
Missing	2 (2%)	0 (0%)	1 (1%)	1 (1%)
Gestation				
Mean (SD)	16.2 (1.2)	16.2 (1.2)	16.2 (1.2)	16.3 (1.2)
Min., max.	14, 20	14, 20	14, 20	14, 20
Missing	2 (2%)	0 (0%)	1 (1%)	1 (1%)
First pregnancy (%)				
Yes	24 (22%)	29 (26%)	29 (26%)	24 (23%)
No	81 (76%)	82 (74%)	82 (73%)	81 (76%)
Missing	2 (2%)	0 (0%)	1 (1%)	1 (1%)

continued

TABLE 6 *Baseline characteristics by the two factor comparisons, Rapid versus no Rapid test and fixed versus variable karyotype result date (cont'd)*

	Rapid test ***n*** **= 83**	**No Rapid test** ***n*** **= 82**	**Fixed date** ***n*** **= 83**	**Variable date** ***n*** **= 82**
Previous pregnancies				
Median	2	2	2	2
Min., max.	1, 8	1, 7	1, 7	1, 8
Missing	2 (2.4%)	1 (1.2%)	2 (2.4%)	1 (1.2%)
Previous miscarriages				
None	51 (61.5%)	56 (68.3%)	53 (63.9%)	54 (65.9%)
Once	25 (30.1%)	22 (26.8%)	26 (31.3%)	21 (25.6%)
More than once	5 (6.0%)	4 (4.9%)	3 (3.6%)	6 (7.3%)
Missing	2 (2.4%)	0 (0.0%)	1 (1.2%)	1 (1.2%)
Previous stillbirth				
Never	80 (96.4%)	78 (95.1%)	80 (96.4%)	78 (95.1%)
Once	1 (1.2%)	4 (4.9%)	2 (2.4%)	3 (3.7%)
More than once	0 (0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	2 (2.4%)	0 (0.0%)	1 (1.2%)	1 (1.2%)
Previous serious abnormality (%)				
Yes	5 (6.0%)	4 (4.9%)	6 (7.2%)	3 (3.7%)
No	76 (91.6%)	78 (95.1%)	76 (91.6%)	78 (95.1%)
Missing	2 (2.4%)	0 (0.0%)	1 (1.2%)	1 (1.2%)
Previous prenatal screening for Down's syndrome (%)				
Yes	37 (44.6%)	42 (51.2%)	42 (50.6%)	37 (45.1%)
No	44 (53.0%)	40 (48.8%)	40 (48.2%)	44 (53.7%)
Missing	2 (2.4%)	0 (0.0%)	1 (1.2%)	1 (1.2%)
Screening type				
Blood test	37	42	42	37
Previous amniocentesis or CVS (%)				
Yes	13 (15.7%)	12 (14.6%)	13 (15.7%)	12 (14.6%)
No	68 (84.9%)	70 (85.4%)	69 (84.1%)	69 (84.1%)
Missing	2 (2.4%)	0 (0.0%)	1 (1.2%)	1 (1.2%)
Do you have children?				
Yes	72 (86.7%)	75 (90.4%)	71 (85.5%)	76 (92.7%)
No	9 (10.8%)	7 (8.5%)	11 (13.3%)	5 (6.1%)
Missing	2 (2.4%)	0 (0.0%)	1 (1%)	1 (1.2%)
How many children?				
Median	2	1	1	2
Min., max.	1, 4	1, 7	1, 7	1, 5
Missing	11 (13.3%)	7 (8.5%)	12 (14.5%)	2 (2.4%)

Twenty of the questions had responses ranging from 1 to 4, but question 18, 'Do you ever feel afraid that you may have any other serious illness?', was not answered with '4 = most of the time'.

Tables 15 and *16* show the frequency that questions were not completed, and it can be seen that there is not a particular question that is completed more or less frequently than any others. Forms that have responses missing for more than three questions were excluded from the analysis. Forms with three or fewer responses missing had had the average for the completed questions imputed.

Table 17 shows the summary statistics for the HAQ at baseline by intervention factor. The score can range from 21 (minimum score) to 84 (maximum score). It can be seen that the scores are evenly balanced across the factors, on the health anxiety score at baseline.

State–Trait Anxiety Inventory (STAI)

The long form of the STAI is made up of 20 questions that form the State Anxiety Scale and 20 questions that form the Trait Anxiety scale. Both scales contain questions that are reverse scored and, if three or more questions are missing for

TABLE 7 *Proportion of women who completed each section of the SOS*

	Rapid test	No Rapid test	Fixed date	Variable date	Total
n	107	111	112	106	218
Husband/partner					
Yes	102 (95%)	110 (99%)	108 (96%)	104 (98%)	212 (97%)
No	4 (4%)	1 (0%)	4 (4%)	1 (0%)	5 (2%)
Missing	1 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Mother					
Yes	96 (90%)	103 (93%)	102 (91%)	97 (92%)	199 (91%)
No	10 (9%)	8 (7%)	10 (9%)	8 (8%)	18 (8%)
Missing	1 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Close friend					
Yes	96 (90%)	105 (95%)	107 (96%)	94 (89%)	201 (92%)
No	10 (9%)	6 (5%)	5 (5%)	11 (10%)	16 (7%)
Missing	1 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Other					
Yes	35 (33%)	43 (39%)	40 (36%)	38 (36%)	78 (36%)
No	71 (66%)	68 (61%)	72 (64%)	67 (63%)	139 (64%)
Missing	1 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Other					
Yes	13 (12%)	20 (18%)	17 (15%)	16 (15%)	33 (15%)
No	91 (85%)	91 (82%)	94 (84%)	88 (83%)	182 (84%)
Missing	3 (3%)	0 (0%)	1 (0%)	2 (2%)	3 (1%)

TABLE 8 *Frequency of the number of sections completed*

Completed sections	Rapid test	No Rapid test	Fixed date	Variable date	Total
n	107	111	112	106	218
0	2 (2%)	0 (0%)	1 (0%)	1 (0%)	2 (1%)
1	0 (0%)	1 (1%)	0 (0%)	1 (0%)	1 (1%)
2	9 (8%)	5 (5%)	7 (6%)	7 (7%)	14 (6%)
3	68 (64%)	66 (60%)	71 (63%)	63 (60%)	134 (62%)
4	13 (12%)	23 (21%)	17 (15%)	19 (18%)	36 (17%)
5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	15 (14%)	16 (14%)	16 (14%)	15 (14%)	31 (14%)

TABLE 9 *Actual emotional support*

	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	5.9 (0.8)	6.0 (0.7)	6.0 (0.7)	5.9 (0.9)
Median (min., max.)	6.0 (2.5, 7.0)	6.1 (3.5, 7.0)	6.0 (4.2, 7.0)	6.0 (2.5, 7.0)
Missing	15	16	16	15

TABLE 10 *Ideal emotional support*

	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	6.5 (0.5)	6.6 (0.5)	6.5 (0.5)	6.5 (0.5)
Median (min., max.)	6.5 (4.8, 7.0)	6.7 (5.0, 7.0)	6.7 (4.8, 7.0)	6.7 (5.2, 7.0)
Missing	15	17	17	15

TABLE 11 *Actual practical support*

	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	5.7 (0.9)	5.8 (0.8)	5.8 (0.7)	5.8 (0.9)
Median (min., max.)	5.8 (1.8, 7.0)	6.0 (3.3, 7.0)	5.8 (1.8, 7.0)	6.0 (1.8, 7.0)
Missing	15	16	16	15

TABLE 12 *Ideal practical support*

	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	6.3 (0.6)	6.3 (0.6)	6.3 (0.6)	6.3 (0.6)
Median (min., max.)	6.3 (4.8, 7.0)	6.5 (4.8, 7.0)	6.3 (4.8, 7.0)	6.5 (4.8, 7.0)
Missing	15	19	17	15

TABLE 13 *Discrepancy between ideal and actual emotional support*

	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	0.7 (0.7)	0.8 (0.9)	0.7 (0.9)	0.7 (0.8)
Median (min., max.)	0.7 (0.0, 3.8)	0.5 (0.0, 6.0)	0.7 (0.0, 6.0)	0.5 (0.0, 3.8)
Missing	15	17	17	15

TABLE 14 *Discrepancy between the ideal and actual practical support*

	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	0.7 (0.89)	0.7 (0.9)	0.7 (0.9)	0.7 (0.8)
Median (min., max.)	0.5 (0.0, 4.0)	0.5 (0.0, 6.0)	0.5 (0.0, 6.0)	0.4 (0.0, 4.0)
Missing	15	17	17	15

TABLE 15 *Frequency of questions not completed*

No. of questions missing	Included	Excluded	Total
0	204	0	204
1	5	0	5
2	1	0	1
4	0	1	1
10	0	2	2
11	0	2	2
21	0	3	3
Total	210	8	218

TABLE 16 *Contents of Health Anxiety Questionnaire*

Question	Missing
1. Do you ever worry about your health?	5
2. Are you ever worried that you may get a serious illness in the future?	5
3. Does the thought of a serious illness ever scare you?	7
4. When you notice an unpleasant feeling in your body, do you tend to find it difficult to think of anything else?	5
5. Do you ever examine your body to find whether there is something wrong?	5
6. If you have an ache or pain do you worry that it may be caused by a serious illness?	5
7. Do you ever find it difficult to keep worries about your health out of your mind?	7
8. When you notice an unpleasant feeling in your body, do you ever worry about it?	6
9. When you wake up in the morning do you find you ever soon begin to worry about your health?	6
10. When you hear of a serious illness or the death of someone you know, does it ever make you more concerned about your own health?	5
11. When you read or hear about an illness on TV or radio does it ever make you think you may be suffering from that illness?	5
12. When you experience unpleasant feelings in your body do you tend to ask friends or family about them?	5
13. Do you tend to read up about illness and diseases to see if you may be suffering from one?	5
14. Do you ever feel afraid of news that reminds you of death (such as funerals, obituary notices)?	5
15. Do you ever feel afraid that you may die soon?	5
16. Do you ever feel afraid that you may have cancer?	5
17. Do you ever feel afraid you might have heart disease?	7
18. Do you ever feel afraid that you may have any other serious illness?	7
19. Have your bodily symptoms stopped you from working during the past 6 months or so?	5
20. Do your bodily symptoms stop you from concentrating on what you are doing?	5
21. Do your bodily symptoms stop you from enjoying yourself?	6

TABLE 17 *Summary of Health Anxiety Questionnaire scores*

	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	32.8 (8.6)	30.7 (6.3)	31.3 (6.9)	32.2 (8.2)
Median (min., max.)	31.0 (22.0, 69.0)	29.4 (21.0, 62.0)	29.4 (21.0, 63.0)	30.0 (22.0, 69.0)
Missing	4	4	3	5

TABLE 18 *Missing data for STAI at baseline*

	State Anxiety			Trait Anxiety		
No. of questions missing	Included	Excluded	Total	Included	Excluded	Total
0	202	0	202	198	0	198
1	13	0	13	11	0	11
2	2	0	2	3	0	3
3	0	0	0	0	1	1
17	0	0	0	0	1	1
20	0	1	1	0	4	4
Total	217	1	218	212	6	218

TABLE 19 *State Anxiety Scale scores by intervention factor*

	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	48.0 (14.0)	47.5 (13.3)	46.4 (14.3)	49.2 (12.8)
Median (min., max.)	47.5 (20.0, 76.0)	47.0 (20.0, 75.0)	43.5 (20.0, 76.0)	50.0 (20.0, 75.0)
Missing	1	0	0	1

TABLE 20 *Trait Anxiety Scale scores by intervention factor*

	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	38.9 (9.4)	36.9 (9.2)	38.5 (9.3)	37.2 (9.3)
Median (min., max.)	37.0 (25.0, 69.0)	36.0 (21.0, 63.0)	37.0 (21.0, 63.0)	36.0 (21.0, 69.0)
Missing	4	2	2	4

either scale, that scale becomes invalidated. *Table 18* shows missing data for the STAI at the baseline.

Tables 19 and *20* show the summary statistics for the State and Trait Anxiety scores by the intervention factor. It can be seen that the anxiety scores are similar across the intervention factors at baseline. A higher score represents higher anxiety.

Compliance with intervention

Twenty-two variable-date women were considered to have minor protocol deviations, as their results were not issued on the day that they became available. However, these women were unaware that their results had been delayed and therefore their anxiety levels had not been affected; as a result, they were not regarded as major protocol violators. This reflects how the intervention would work in practice as women not given a fixed date may be more difficult to contact. However, this does affect the difference in the mean waiting time between fixed- and variable-date women, which is reduced. Therefore, a sensitivity analysis around the inclusion of these women was carried out to check the robustness of the ITT results.

The reasons for the delays in contacting women were as follows:

- 16 were unable to be contacted until the following day.
- 2 were unable to be contacted until after the weekend.
- 1 problem with the fax machine delayed the result for 2 days.
- 1 woman was on holiday and requested not to be contacted until afterwards, delaying the result for 6 days.
- 1 woman was unable to be contacted until her next scan.
- 1 result was delayed for 2 days (reason not known).

It was expected that women may ask at the time of giving consent about the process for issuing abnormal test results. Only those women enquiring were told that all abnormal results would be issued by the consultant as soon as they became available and would not be delayed until day 18. Those women randomised to receive their karyotype result on a fixed day having this information may therefore begin to anticipate a normal result as day 18 draws nearer on the basis that they have not been contacted with an abnormal result. This information would not affect women randomised to the variable date. Midwives were asked to record if a woman had asked about the issuing of abnormal results. *Table 21* shows the number of women asking if an abnormal result would be given early.

TABLE 21 *Women asking if an abnormal result would be given early*

	Rapid test	No Rapid test	Total
Fixed date	9	8	17
Variable date	9	7	16
Total	18	15	33

TABLE 22 *Number of days after the amniocentesis that karyotype results were issued*

Day	Fixed date	Variable date	Total
10	0	1	1
11	0	2	2
12	0	0	0
13	0	4	4
14	0	13	13
15	0	26	26
16	2	25	27
17	37	17	54
18	51	9	60
19	21	4	25
20	1	1	2
21	0	2	2
Results not issued	0	2	2
Total	112	106	218

Time to karyotype results

Table 22 summarises the number of days after the amniocentesis that the karyotype results were

TABLE 23 *Days from amniocentesis day to karyotype result – by intervention factor*

	Rapid test *n* = 107	No Rapid test *n* = 111	Fixed date *n* = 112	Variable date *n* = 106
Mean (SD)	16.9 (1.8)	16.8 (1.7)	17.8 (0.8)	15.8 (1.8)
Median	17.0	17.0	18.0	16.0
Min., max.	10.0, 21.0	11.0, 19.0	16.0, 20.0	10.0, 21.0
Missing	2	0	0	2

TABLE 24 *Anxiety scores for each of the intervention factors*

Intervention	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	11.0 (2.4)	13.3 (3.4)	11.9 (3.1)	12.3 (3.2)
Median (min., max.)	11.2 (5.8, 17.1)	13.2 (6.1, 21.7)	11.8 (6.1, 18.9)	12.1 (5.8, 21.7)
Missing	10	27	16	21

issued by the intervention factor fixed versus variable date. About 97% (109/112) fixed-date women received their karyotype result on days 17–19, that is, day 18 ± 1, with the earliest result being issued on day 16 and the latest on day 20. As had been expected, variable-date women received their karyotype result between days 10 and 21, with 81/106 (76%) becoming available between days 14 and 17. *Table 23* summarises the results for the two intervention factors.

Missing data

The data for this trial are based on woman-completed diaries, therefore the level of missing data, how to handle any missing data and the imputation of missing data can have an impact on the outcome of the trial. Appendix 8 details the rate of missing diaries, the level of missing data for each of the end-points and the method and reasons for the choice of imputation used for each of the end-points.

Primary end-point

Interaction term

Using a linear regression model, no interaction term was found [analysis of variance (ANOVA) ($p = 0.56$)], therefore the analysis follows the factorial design of the trial.

Average anxiety during the waiting period

Table 24 summarises the SAUC of the daily anxiety scores on a 19-point scale with scores ranging from 6 to 24. A higher score shows higher anxiety.

Unadjusted analysis

An unadjusted analysis was undertaken using a linear regression procedure in SAS; the factorial design of the trial was taken into account and each of the factors within the factorial design was adjusted for, that is, Rapid test versus no Rapid test and fixed versus variable date.

Table 25 shows a statistically significant reduction ($p < 0.0001$) in the average anxiety during the waiting period for women who have had a rapid test. The standardised effect size of 0.77 is a moderate effect size;[32] the 95% CI indicates that the difference is in fact a moderate to good reduction in anxiety for women having a Rapid test, and the standardised effect size is a measure of the clinical significance of the difference.

Anxiety levels during the waiting period for women receiving a normal karyotype result on a fixed date are not statistically significantly different at the 5% level from women receiving a normal karyotype result on a variable date. The difference in the means is 0.37 on the anxiety scale score in favour of the fixed date; however, the 95% CI shows that there could be a reduction in anxiety in either direction. This analysis only has sufficient power to find a moderate to large effect size. The standardised effect size of 0.13 and its CI indicate that the difference in anxiety could be small in favour of variable-date women to moderate in favour of fixed-date women. These results are not conclusive for this end-point. *Table 25* shows the results of the primary end-point analysis only adjusting for the factorial design.

TABLE 25 *Results of the primary end-point analysis, adjusting for the factorial design*

Comparison	Included in analysis	Missing	Adjusted mean (SE)	Scale score difference (95% CI)	*p*-Value	Standardised effect size (95% CI)
Rapid test vs no Rapid test	181	37	11.05 (0.30) 13.29 (0.32)	2.24 (1.38 to 3.09)	<0.0001	0.77 (0.47 to 1.06)
Fixed date vs variable date	181	37	11.98 (0.30) 12.36 (0.32)	–0.37 (–1.23 to 0.49)	0.3954	–0.13 (–0.42 to 0.17)

SE, standard error.

Sensitivity analyses

The results of the sensitivity analyses are shown in Appendix 9. The results confirm the results from the primary analysis, demonstrating the robustness of the results.

Adjusted analysis

An adjusted analysis was undertaken using a linear regression procedure in SAS. The primary end-point was adjusted for each of the factors within the factorial design, that is, Rapid test versus no Rapid test and fixed versus variable date; the additional variables were the minimisation factors, that is woman's age at randomisation (<35, ≥35 years), most senior person present (29 levels), plus the other covariates that had been identified as important factors: reasons for having an amniocentesis (maternal age, triple test risk, single soft marker for Down's syndrome, parental anxiety) and previous problems (women who had had a previous miscarriage or a still birth/baby that died or a baby with a previous abnormality), and gestation (weeks).

The analysis was adjusted for the most senior person present as it was one of the minimisation factors; however, as this factor is at 29 levels, the estimates are questionable, hence interpretation is complex and, as significant differences between clinicians are of no interest, the results have not been presented.

Table 26 shows the adjusted mean, the mean scale score difference, *p*-value and the standardised effect size for each of the categorical factors included in the adjusted analysis. *Table 27* shows the parameter estimate, standard error and *p*-value for the continuous factor in the adjusted analysis.

The Rapid test vs no Rapid test comparison shows a highly statistically significant reduction at the 1% level in favour of women receiving a rapid test; the standardised effect size shows that this is a moderate difference and the 95% CI shows that this is a moderate to good difference.

The fixed versus variable karyotype result date comparison shows a possible trend towards women receiving the karyotype result on a fixed date having less anxiety; the 95% CI around the standardised effect size shows that this could be a very small difference in the opposite direction up to a moderate difference in favour of fixed-date women, but the result of this comparison is not conclusive. The analysis was only powered to find a moderate effect size.

The comparison between under 35-year-olds at randomisation versus those aged 35 years and over shows a borderline significant reduction in anxiety ($p = 0.06$) in favour of the latter group. The 95% CI around the effect size shows that this could be a small reduction in the opposite direction to a very large reduction in favour of those aged 35 years and over.

The comparison between the three categories of education level shows no significant differences. The 95% CIs around the standardised effect size for each of the three comparisons indicate that there could be a small to moderate reduction in favour of the less educated a person is to a large reduction in favour of the more educated a person is.

The comparison between women having had a previous problem (a previous problem is defined as a previous miscarriage or a still birth/baby that died or a baby with a previous abnormality) again shows borderline significance ($p = 0.08$), with a reduction in anxiety in favour of women not having a previous problem. The standardised effect size indicates that this is a moderate difference; however, the 95% CI shows that it could be a large reduction in favour of no previous problems to a very small reduction in the opposite direction.

TABLE 26 *Results of the adjusted analysis – categorical variables*

Comparison	Included in analysis	Missing	Adjusted mean (SE)	Scale score difference (95% CI)	*p*-Value	Standardised effect size (95% CI)
Rapid test vs no Rapid test	135	83	12.51 (0.95) 14.88 (0.94)	2.36 (1.18 to 3.55)	0.0001	0.77 (0.39 to 1.16)
Fixed date vs variable date	135	83	13.18 (0.93) 14.20 (0.96)	–1.02 (–2.21 to 0.18)	0.0933	–0.33 (–0.73 to 0.06)
Age at randomisation (years) <35 vs ≥35	135	83	14.54 (1.02) 12.85 (0.97)	1.68 (–0.06 to 3.43)	0.0588	0.55 (–0.20 to 1.13)
Qualifications						
None (1)	135	83	14.66 (1.28)	(1 vs 2) 1.32 (–1.22 to 3.86)	0.4354	0.43 (–0.40 to 1.27)
GCSE (2)			13.34 (0.98)	(1 vs 3) 1.59 (–0.79 to 3.97)	0.2359	0.52 (–0.26 to 1.30)
Post-16 (3)			13.07 (0.82)	(2 vs 3) 0.27 (–1.35 to 1.90)	0.9170	0.09 (–0.44 to 0.62)
Previous problem						
No Yes	135	83	13.15 (0.91) 14.23 (0.98)	–1.08 (–2.27 to 0.12)	0.0776	–0.35 (–0.75 to 0.04)
Reason for amniocentesis						
Maternal age						
Yes No	135	83	13.04 (1.26) 14.34 (0.92)	–1.31 (–3.86 to 1.25)	0.3133	–0.43 (–1.27 to 0.41)
Triple						
Yes No	135	83	13.59 (1.33) 13.79 (0.97)	–0.20 (–3.16 to 2.76)	0.8919	–0.07 (–1.04 to 0.90)
Down's syndrome						
Yes No	135	83	14.39 (1.44) 13.0 (0.68)	1.39 (–1.34 to 4.13)	0.3140	0.46 (–0.44 to 1.35)
Parental anxiety						
Yes No	135	83	13.70 (1.25) 13.68 (0.86)	0.02 (–2.33 to 2.36)	0.9874	0.01 (–0.76 to 0.78)

SE, standard error.

TABLE 27 *Results of the adjusted analysis – continuous variable*

	Included in analysis	Missing	Parameter estimate	Standard error	*p*-Value
Gestation (weeks)	135	83	–0.6425	0.33	0.0534

None of the reasons for having the amniocentesis comparisons show any significant differences in anxiety levels. The 95% CIs around the standardised effect sizes indicate that there could be a moderate to large difference in either direction for maternal age, triple test result, Down's syndrome and parental anxiety.

Gestation (number of weeks of pregnancy) is a continuous variable and has borderline significance at the 5% level. The parameter estimate indicates that with each additional week of pregnancy anxiety levels are reduced.

Table 26 shows a statistically significant reduction at the 1% level in the average anxiety during the waiting period for women who have had a Rapid test. The standardised effect size of 0.77 is a moderate effect size; the 95% CI indicates that the difference is a moderate to good reduction in anxiety for women having a rapid test, and the

TABLE 28 *Primary end-point analysis, adjusted for the baseline quality of life questionnaires*

Comparison	Included in analysis	Missing	Adjusted mean (SE)	Scale score difference (95% CI)	*p*-Value	Standardised effect size (95% CI)
Rapid test vs no Rapid test	155	63	11.03 (0.26) 13.30 (0.28)	2.27 (1.51 to 3.03)	<0.0001	0.97 (0.64 to 1.29)
Fixed date vs variable date	155	63	12.14 (0.26) 12.20 (0.28)	–0.06 (–0.82 to 0.71)	0.8837	–0.02 (–0.35 to 0.30)

TABLE 29 *Each quality of life measure included in the model and adjusted for all the others*

	Included in analysis	Missing	Parameter estimate	Standard error	*p*-Value
STAI Trait	155	63	0.0406	0.0292	0.1669
STAI State	155	63	0.1193	0.0161	<0.0001
Discrepancy emotional support	155	63	–0.3478	0.4353	0.4256
Discrepancy practical support	155	63	0.4900	0.4542	0.2824
HAQ score	155	63	–0.0311	0.0325	0.3403

standardised effect size is a measure of the clinical significance of the difference.

Anxiety levels during the waiting period for women receiving a normal karyotype result on a fixed date are not statistically significantly different at the 5% level from those for women receiving a normal karyotype result on a variable date. The difference in the means is 1.02 on the anxiety scale score in favour of the fixed date; however, the 95% CI shows that there could be a reduction in anxiety in either direction. This final analysis only has sufficient power to find a moderate to a large effect size. The standardised effect size of 0.33 and its 95% CI indicate that the difference in anxiety could be very small to moderate. These results are not conclusive for this end-point.

Adjusting the primary end-point analysis by the baseline quality of life questionnaires

Table 28 summarises the adjusted means for the primary end-point, the SAUC after adjusting the analysis for the baseline quality of life questionnaires, the STAI Trait and State scores, the SOS scores using the discrepancy in emotional and practical support and the score from the HAQ. The table shows that there is a statistically significant reduction in anxiety for Rapid test women and no evidence of a difference for fixed- versus variable-date women.

Table 29 shows the significance of each measure after adjusting for all the other measures. It can be seen that the STAI State baseline score is highly significant in predicting anxiety scores. Each of the measures is a continuous variable; the parameter estimate indicates that for each additional unit score on each measure the anxiety changes by the parameter estimate, that is, it increases on the STAI State score but decreases on the HAQ score. A higher score on the STAI Trait and State scales and discrepancy in practical support will increase anxiety; each additional unit on the discrepancy in emotional support measures and the HAQ will reduce anxiety.

Secondary end-points

Many of the secondary end-points focus on the pattern of anxiety during the waiting period by examining more closely various periods of time within that waiting period. Women with missing data were only excluded from the end-points if they had insufficient data for that endpoint, therefore the populations may vary slightly between secondary end-points.

The original power calculations were based on the primary end-point; however, as a result of the reduced sample size, the trial is only powered sufficiently to find a moderate to large difference in anxiety.

Each of the secondary end-points is presented in this section with summary statistics; the formal statistical analysis for all secondary end-points is

TABLE 30 *Frequency with which women reach their peak anxiety score, by intervention group*

Frequency	Rapid test	No Rapid test	Fixed date	Variable date	Total
1	73 (68%)	56 (50%)	64 (57%)	65 (61%)	129 (59%)
2	23 (22%)	22 (20%)	26 (23%)	19 (18%)	45 (21%)
3	2 (2%)	2 (2%)	3 (3%)	1 (1%)	4 (2%)
4	2 (2%)	4 (4%)	5 (4%)	1 (1%)	6 (3%)
5	0 (0%)	3 (3%)	2 (2%)	1 (1%)	3 (1%)
6	0 (0%)	1 (1%)	0 (0%)	1 (1%)	1 (0%)
7	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
8	0 (0%)	2 (2%)	1 (1%)	1 (1%)	2 (1%)
9	0 (0%)	1 (1%)	0 (0%)	1 (1%)	1 (0%)
Missing	7 (7%)	20 (18%)	11 (10%)	16 (15%)	27 (12%)
Total	107	111	112	106	218

TABLE 31 *Summary statistics of peak anxiety scores by intervention factor*

Intervention	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	19.4 (3.5)	20.3 (3.7)	19.7 (3.8)	20.0 (3.5)
Median (min., max.)	20.0 (12.0, 24.0)	21.0 (9.0, 24.0)	20.0 (9.0, 24.0)	21.0 (11.0, 24.0)
Missing	7	20	11	16

presented at the end of the section to aid the reader in comparing end-points and to reduce repetition.

Peak anxiety during the waiting period

This secondary end-point looks at the woman's maximum anxiety score during the waiting period, from amniocentesis test day to karyotype result day.

The daily anxiety scale score can range from 6 to 24. The number of times a woman may reach her maximum score is not taken into account in the analysis, however. *Table 30* summarises the frequency of times a woman does reach her peak anxiety score. It can be seen that a large proportion of women, 129/218 (59%), only reach their maximum anxiety score once; however, one woman reached her maximum score on nine separate days.

Table 31 shows the summary statistics of peak anxiety scores, by intervention factor.

Length of time to the peak anxiety

This secondary end-point looks at the length of time until the woman reaches her maximum score for the first time. Again, this analysis does not consider how many times that maximum score is recorded. No imputation has been carried out.

Table 32 summarises the days that women reach their first peak anxiety score; 49/218 (22%) women reach their peak score on day 1, that is, amniocentesis test day itself. A relatively smaller proportion of no Rapid test fixed-date women (9%) compared with more than 20% for the other groups reach their maximum anxiety scores on day 1. 31/218 (14%) reach their peak scores on either day 2 or 3; four of these 31 women do not have data for day 1. 12/218 (6%) reach their peak anxiety score on day 17, which is the day before the karyotype result for fixed date women. A relatively larger proportion of no Rapid test, fixed-date women (12%) compared with less than 6% for the other groups reach their peak anxiety score on day 17, the day before their karyotype result.

Table 33 shows the summary statistics of length of time to first peak by intervention factor.

Total anxiety in 11 days following amniocentesis

This secondary end-point examines the woman's anxiety for the 11 days immediately following the amniocentesis test day itself, including the amniocentesis test day. This timeframe was thought to be important as it compares the period of time that is believed to carry the highest risk of miscarriage.

Table 34 shows the summary statistics for the total anxiety scores for the 11 days following the amniocentesis by intervention factor.

TABLE 32 *Frequency of day of peak daily anxiety score by intervention factor*

Day	Rapid test	No Rapid test	Fixed date	Variable date	Overall total
1	32 (30%)	17 (15%)	26 (23%)	23 (22%)	49 (22%)
2	13 (12%)	2 (2%)	6 (5%)	9 (8%)	15 (7%)
3	9 (8%)	7 (6%)	9 (8%)	7 (7%)	16 (7%)
4	4 (4%)	5 (5%)	3 (3%)	6 (6%)	9 (4%)
5	4 (4%)	4 (4%)	2 (2%)	6 (6%)	8 (4%)
6	4 (4%)	3 (3%)	5 (4%)	2 (2%)	7 (3%)
7	3 (3%)	3 (3%)	1 (1%)	5 (5%)	6 (3%)
8	2 (2%)	4 (4%)	1 (1%)	5 (5%)	6 (3%)
9	3 (3%)	3 (3%)	1 (1%)	5 (5%)	6 (3%)
10	3 (3%)	4 (4%)	4 (4%)	3 (3%)	7 (3%)
11	3 (3%)	0 (0%)	0 (0%)	3 (3%)	3 (1%)
12	3 (3%)	3 (3%)	4 (4%)	2 (2%)	6 (3%)
13	3 (3%)	4 (4%)	4 (4%)	3 (3%)	7 (3%)
14	3 (3%)	4 (4%)	6 (5%)	1 (1%)	7 (3%)
15	3 (3%)	2 (2%)	3 (3%)	2 (2%)	5 (2%)
16	2 (2%)	4 (4%)	2 (2%)	4 (4%)	6 (3%)
17	2 (2%)	10 (9%)	8 (7%)	4 (4%)	12 (6%)
18	2 (2%)	4 (4%)	6 (5%)	0 (0%)	6 (3%)
19	1 (1%)	7 (6%)	8 (7%)	0 (0%)	8 (4%)
20	1 (1%)	1 (1%)	2 (2%)	0 (0%)	2 (1%)
Missing	7 (7%)	20 (18%)	11 (10%)	16 (15%)	27 (12%)
Total	107	111	112	106	218

TABLE 33 *Summary statistics of peak anxiety scores by intervention factor*

Intervention	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	5.8 (5.5)	9.4 (6.6)	8.7 (7.0)	6.1 (5.1)
Median (min., max.)	3.0 (1.0, 20.0)	9.0 (1.0, 20.0)	6.0 (1.0, 20.0)	4.5 (1.0, 17.0)
Missing	7	20	11	16

TABLE 34 *Summary statistics for anxiety scores for 11 days following amniocentesis by intervention factor*

Intervention	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	131.7 (30.0)	152.0 (30.0)	137.6 (35.6)	144.8 (36.7)
Median (min., max.)	132.0 (73.0, 220.0)	149.8 (70.4, 251.0)	137.0 (70.4, 225.0)	144.5 (73.0, 251.0)
Missing	9	27	16	20

Average anxiety from day 12 to karyotype results day

This secondary end-point examines the average anxiety from day 12 to karyotype results day, which is the last few days up to a maximum of 1 week of the waiting period. This end-point focuses on the period immediately prior to the karyotype result, after the period of highest risk of miscarriage has passed. This analysis uses the SUAC.

Table 35 shows the summary statistics of the average anxiety from day 12 to results day by intervention factor.

Total anxiety from amniocentesis day to day 21

This secondary end-point focuses on the total anxiety from amniocentesis test day through to day 21 following the amniocentesis. All women

TABLE 35 *SAUC for women from day 12 to results day by intervention factor*

Intervention	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	11.4 (3.0)	14.5 (4.2)	12.9 (3.81)	12.9 (4.1)
Median (min., max.)	11.0 (6.0, 18.2)	11.0 (6.0, 18.2)	12.8 (6.0, 22.9)	12.7 (6.0, 22.8)
Missing	11	22	13	20

TABLE 36 *Summary statistics for total anxiety over 21 days by intervention factor*

Intervention	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	239.0 (50.2)	278.6 (69.9)	256.0 (63.9)	259.7 (62.9)
Median (min., max.)	244.0 (133.0, 365.0)	278.0 (133.4, 454.0)	251.0 (133.4, 416.0)	255.0 (133.0, 454.0)
Missing	16	30	17	29

TABLE 37 *Summary statistics for total anxiety for 4 days following amniocentesis by intervention factor*

Intervention	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	54.8 (13.4)	57.4 (14.9)	55.1 (14.7)	57.0 (13.5)
Median (min., max.)	53.5 (27.0, 96.0)	58.0 (24.0, 92.0)	54.0 (24.0, 96.0)	58.3 (31.0, 92.0)
Missing	7	24	13	18

TABLE 38 *Summary statistics for anxiety scores 7 days prior to karyotype result by intervention factor*

Intervention	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	76.9 (22.2)	100.1 (30.7)	85.9 (27.9)	90.7 (30.2)
Median (min., max.)	73.3 (36.0, 143.0)	98.0 (42.0, 167.0)	86.5 (36.0, 158.0)	90.0 (42.0, 167.0)
Missing	11	22	12	21

will have received their normal karyotype result by day 21. This end-point compares the anxiety levels over a fixed waiting period of 21 days; all women will have reached their karyotype result by this date.

Table 36 shows the summary of total anxiety over 21 days following the amniocentesis by intervention factor.

Total anxiety for the first 4 days

This secondary end-point looks at the total anxiety for women for the first 4 days following the amniocentesis (including amniocentesis day).

Table 37 shows the summary of the total anxiety scores for the 4 days following the amniocentesis, including day 1 (amniocentesis day), by intervention factor.

Total anxiety for the 7 days prior to karyotype results day

This secondary end-point compares the total anxiety for women in the last 7 days that they are waiting for their normal karyotype result. The fixed-date women will know they have 7 days left to wait for their results; however, the variable-date women do not know how long they have to wait, but it is likely to be less time.

Table 38 shows the summary statistics of the total anxiety scores for the 7 days prior to the karyotype result, by intervention factor.

Recalled anxiety

Women were asked to complete a follow-up questionnaire 1 month after they had received their karyotype result. The clinically important timeframe for recalled anxiety had been defined

TABLE 39 *Forms received within an acceptable time frame by intervention factor*

	Rapid test	No Rapid test	Fixed date	Variable date	Total
22–24 days	2 (2%)	2 (2%)	3 (3%)	1 (1%)	4 (2%)
25–49 days	93 (87%)	82 (74%)	89 (80%)	86 (81%)	175 (80%)
>49 days	4 (4%)	9 (8%)	7 (6%)	6 (6%)	13 (6%)
Missing	6 (6%)	18 (16%)	13 (12%)	11 (10%)	22 (10%)
Withdrawn prior to follow-up	2 (2%)	0 (0%)	0 (0%)	2 (2%)	4 (2%)
Total	107	111	112	106	218

TABLE 40 *Frequency of score for recalled anxiety 10–12 days after amniocentesis test by intervention factor*

Score	Rapid test	No Rapid test	Fixed date	Variable date	Total
0	1 (1%)	1 (1%)	1 (1%)	1 (1%)	2 (1%)
1	1 (1%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
2	5 (5%)	6 (5%)	9 (8%)	2 (2%)	11 (5%)
3	14 (13%)	5 (5%)	12 (11%)	7 (7%)	19 (9%)
4	4 (4%)	7 (6%)	3 (3%)	8 (8%)	11 (5%)
5	11 (10%)	7 (6%)	9 (8%)	9 (9%)	18 (8%)
6	14 (13%)	12 (11%)	12 (11%)	14 (13%)	26 (12%)
7	8 (8%)	11 (10%)	10 (9%)	9 (9%)	19 (9%)
8	11 (10%)	11 (10%)	10 (9%)	12 (11%)	22 (10%)
9	9 (8%)	5 (5%)	8 (7%)	6 (6%)	14 (6%)
10	15 (14%)	16 (14%)	13 (12%)	18 (17%)	31 (14%)
Missing	14 (13%)	30 (27%)	24 (21%)	20 (19%)	44 (20%)
Total	107	111	112	106	218

TABLE 41 *Summary statistics for recalled anxiety 10–12 days after the amniocentesis by intervention factor*

Intervention	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	6.3 (2.7)	6.6 (2.6)	6.1 (2.8)	6.7 (2.5)
Median (min., max.)	6 (0, 10)	7 (0, 10)	6 (0, 10)	6 (0, 10)
Missing	14	30	24	20

as days 25–49 inclusive. Therefore, forms completed outside this time frame were excluded from the analysis. *Table 39* shows the frequency of forms completed too early, within the acceptable time frame, and too late by intervention factor.

Women were asked to recall their anxiety from the period around 10–12 days after they had had their amniocentesis test, and then to think about the 2–3 days just before they received their final karyotype result. Women were asked to circle a number between 0 and 10, where 0 represented not at all anxious and 10 represented very anxious.

Recalled anxiety, thinking about the 10–12 days following the amniocentesis test

Table 40 shows the frequency of each score between 0 and 10 for the recalled anxiety at 10–12 days following the amniocentesis by intervention factor. It can be seen that overall recalled anxiety at 10–12 days follows a similar pattern across the groups; a small percentage (1%) of women have recorded their recalled anxiety at zero, the highest percentage of women (14%) recall the maximum anxiety of 10. More variable-date women recorded a maximum anxiety than fixed-date women at 10–12 days. Approximately half [86/174 (49%)] of women who completed the question recalled their anxiety in excess of 6 (high anxiety).

Table 41 shows the summary statistics of scores for recalled anxiety 10–12 days after the amniocentesis, by intervention factor.

Recalled anxiety, thinking about 2–3 days prior to receiving karyotype result

Table 42 shows the frequency of each score between 0 and 10 for the recalled anxiety at

TABLE 42 *Frequency of score for recalled anxiety 2–3 days prior to karyotype result, by intervention factor*

Score	Rapid test	No Rapid test	Fixed	Variable	Total
0	3 (3%)	0 (0%)	2 (2%)	1 (1%)	3 (1%)
1	1 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
2	10 (9%)	0 (0%)	5 (4%)	5 (5%)	10 (5%)
3	15 (14%)	1 (1%)	10 (9%)	6 (6%)	16 (7%)
4	3 (3%)	3 (3%)	5 (4%)	1 (1%)	6 (3%)
5	10 (9%)	2 (2%)	5 (4%)	7 (7%)	12 (6%)
6	11 (10%)	3 (3%)	8 (7%)	6 (6%)	14 (6%)
7	7 (7%)	6 (5%)	9 (8%)	4 (4%)	13 (6%)
8	12 (11%)	14 (13%)	8 (7%)	18 (17%)	26 (12%)
9	5 (5%)	12 (11%)	10 (9%)	7 (7%)	17 (8%)
10	16 (15%)	41 (37%)	27 (24%)	30 (28%)	57 (26%)
Missing	14 (13%)	29 (26%)	23 (21%)	20 (19%)	43 (20%)
Total	107	111	112	106	218

TABLE 43 *Summary statistics for recalled anxiety 2–3 days prior to receiving karyotype result by intervention factor*

Intervention	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	5.8 (3.0)	8.7 (1.7)	7.0 (2.9)	7.4 (2.8)
Median (Min., max.)	6 (0.0, 10.0)	9.5 (3.0, 10.0)	8.0 (0.0, 10.0)	8.0 (0.0, 10.0)
Missing	14	29	23	20

TABLE 44 *Summary statistics for anxiety at 1-month follow-up by intervention factor*

Intervention	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Mean (SD)	9.2 (3.5)	8.3 (2.9)	8.5 (2.9)	9.0 (3.6)
Median (min., max.)	8.0 (6.0, 21.0)	7.0 (6.0, 19.0)	8.0 (6.0, 18.0)	8.0 (6.0, 21.0)
Missing	14	31	24	21

2–3 days prior to receiving the karyotype result by intervention factor. Approximately one-quarter of women recall maximum anxiety (score 10) at 2–3 days prior to the karyotype result; 37% of no Rapid test women recall maximum anxiety compared with 15% of Rapid test women, and 24.1% for fixed-date women compared with 28% for variable-date women.

Table 43 shows the summary statistics of score for recalled anxiety at 2–3 days prior to receiving the karyotype result by intervention factor.

Anxiety at 1-month follow-up

At the 1-month follow-up, women were also asked to complete their anxiety on the day they completed the form, using the same format that had been used in the daily dairy, the short form of the STAI.

Table 44 shows the summary statistics of anxiety scores at the 1-month follow-up, by intervention factor.

A linear regression analysis adjusting for each of the intervention factors was used to compare the anxiety for each of the secondary end-points for Rapid versus no Rapid test women and for fixed- versus variable-date karyotype result women. *Table 45* shows the standardised effect size and its 95% CI for each of the secondary end-points.

Table 45 shows that for the peak anxiety during the waiting period, the standardised effect size indicates a small reduction in peak anxiety for Rapid test women; the 95% CI indicates that this could be a moderate reduction for Rapid test women to a very small reduction for no Rapid test women, indicating some evidence for a statistical

difference in anxiety. It also shows on average a small reduction in favour of fixed-date women, although the 95% CI indicates that there is no evidence for a statistical difference.

Table 45 shows that for total anxiety in the 11 days following the amniocentesis, the standardised effect size and its 95% CI indicate that there is a moderate to large reduction in anxiety for women who receive a Rapid test result. The 95% CI around the standardised effect size for the fixed- versus variable-date comparison indicates that there is no evidence for a difference in anxiety.

Table 45 shows that for average anxiety from day 12 to standard culture results day using SAUC, the standardised effect size and its 95% CI indicate that there is a moderate to large reduction in anxiety for Rapid test women. The 95% CI around the standardised effect size for the fixed- versus variable-date comparison shows that there could be a small reduction in anxiety in either direction.

Table 45 shows that for total anxiety from amniocentesis day to day 21, the standardised effect size and its 95% CI indicate that this is a moderate to large difference in favour of Rapid test women. The 95% CI around the standardised effect size for the fixed- versus variable-date comparison indicates that there is no evidence for a statistical difference in anxiety levels.

Table 45 shows that for total anxiety for the first 4 days, the 95% CI around the standardised effect size for both comparisons indicates that there is no evidence for a difference in anxiety levels.

Table 45 shows that for total anxiety for 7 days prior to standard culture results day, the standardised effect size and its 95% CI show a reduction in anxiety levels for Rapid test women. The standardised effect size and its 95% CI indicate that this is a moderate to a large reduction. The 95% CI around the standardised effect size for the fixed- versus variable-date comparison indicates there is no evidence for a difference in anxiety.

Table 45 shows that for recalled anxiety at 10–12 days after amniocentesis the 95% CI around the standardised effect size indicates that there is no evidence for a statistical difference in recalled anxiety between the Rapid and no Rapid test women and the fixed- variable-date women.

Table 45 shows that for recalled anxiety at 2–3 days prior to receiving standard culture result, the standardised effect size and its 95% CI show a large reduction in anxiety for rapid test women. The 95% CI around the standardised effect size for fixed- versus variable-date women indicates that there is no evidence for a statistical difference.

Table 45 shows that for anxiety at 1-month follow-up, the standardised effect size indicates that there is a small to moderate reduction in anxiety in favour of women not having a Rapid test. The 95% CI around the standardised effect size for the fixed- versus variable-date comparison shows that there is no evidence for a difference.

A Cox proportional hazards model was used to analyse the time to peak anxiety, adjusting for each of the intervention factors within the factorial design of the trial. *Table 46* shows the hazard ratio and 95% CI for each comparison, Rapid Test versus no Rapid test, and fixed- versus variable-date karyotype result. The hazard ratio shows that Rapid test women are 62% more likely to reach their peak anxiety level sooner than no Rapid test women; the 95% CI shows this could range from 1.2 to 2.2 times more likely to reach the peak anxiety sooner. The hazard ratio for the fixed- versus variable-date comparison shows that fixed-date women are less likely to reach their peak anxiety sooner; the 95% CI suggests that this is between 0.45 and 0.83 times more likely.

Adverse events

Table 47 summarises the five adverse events by intervention group. One woman had a miscarriage 49 days after the amniocentesis test; it was not related to the amniocentesis and occurred after the amniocentesis result. Her diary had been completed for 24 days and returned, and as she had also been issued with a normal karyotype result this woman was included in the analysis.

One amniocentesis fluid sample was not received by the laboratory; this woman was excluded from the analysis post-randomisation and was reported as a failure of the karyotype result; this reflects what happens in practice. This woman subsequently decided not to have a second amniocentesis.

One woman had a ruptured membrane, leading to a miscarriage, and was excluded post-randomisation.

TABLE 45 *Adjusted analysis of all the secondary end-points*

Comparison	Included in analysis	Missing	Adjusted mean (SE)	Scale score difference (95% CI)	Standardised effect size (95% CI)
Peak anxiety during the waiting period					
Rapid test vs no Rapid test	191	27	19.41 (0.36) 20.26 (0.38)	–0.85 (–1.87 to 0.18)	–0.24 (–0.52 to 0.05)
Fixed vs variable	191	27	19.69 (0.36) 19.97 (0.38)	–0.28 (–1.32 to 0.76)	–0.08 (–0.36 to 0.21)
Total anxiety in 11 days following amniocentesis					
Rapid test vs no Rapid test	182	36	131.93 (3.52) 152.07 (3.80)	–20.14 (–30.36 to –9.93)	–0.58 (–0.87 to –0.29)
Fixed date vs variable date	182	36	138.68 (3.56) 145.31 (3.76)	–6.63 (–16.83 to 3.57)	–0.19 (–0.48 to 0.10)
Average anxiety from day 12 to standard culture results day					
Rapid test vs no Rapid test	185	33	11.42 (0.37) 14.53 (0.38)	–3.10 (–4.15 to –2.05)	–0.86 (–1.15 to –0.57)
Fixed date vs variable date	185	33	13.01 (0.36) 12.94 (0.39)	0.06 (–0.99 to 1.11)	0.02 (–0.27 to 0.31)
Total anxiety from amniocentesis day to day 21					
Rapid vs no Rapid test	172	46	239.14 (6.37) 278.67 (6.72)	–39.53 (–57.77 to –21.29)	–0.65 (–0.96 to –0.35)
Fixed date vs variable date	172	46	257.85 (6.22) 259.95 (6.89)	–2.10 (–20.41 to 16.21)	–0.03 (–0.34 to 0.27)
Total anxiety for the first 4 days					
Rapid test vs no Rapid test	187	31	54.85 (1.41) 57.42 (1.52)	–2.57 (–6.65 to 1.52)	–0.18 (–0.47 to 0.11)
Fixed date vs variable date	187	31	55.17 (1.42) 57.10 (1.51)	–1.93 (–6.02 to 2.15)	–0.14 (–0.43 to 0.15)
Total anxiety for the 7 days prior to standard culture results day					
Rapid test vs no Rapid test	185	33	77.12 (2.72) 100.23 (2.82)	–23.11 (–30.84 to –15.38)	–0.87 (–1.16 to –0.58)
Fixed date vs variable date	185	33	86.55 (2.66) 90.80 (2.89)	–4.24 (–11.99 to 3.51)	–0.16 (–0.45 to 0.13)
Recalled anxiety 10–12 days after amniocentesis					
Rapid test vs no Rapid test	174	44	6.27 (0.27) 6.57 (0.29)	–0.30 (–1.09 to 0.49)	–0.11 (–0.41 to 0.19)
Fixed date vs variable date	174	44	6.10 (5.55) 6.74 (0.28)	–0.64 (–1.43 to 0.15)	–0.24 (–0.54 to 0.06)
Recalled anxiety 2–3 days prior to receiving standard culture result					
Rapid test vs no Rapid test	175	43	5.85 (0.25) 8.73 (0.27)	–2.87 (–3.61 to –2.14)	–1.17 (–1.47 to –0.87)
Fixed date vs variable date	175	43	7.05 (0.26) 7.53 (0.26)	–0.48 (–1.22 to 0.25)	–0.20 (–0.50 to 0.10)
Anxiety at 1-month follow-up					
Rapid test vs no Rapid test	173	45	9.23 (0.34) 8.28 (0.36)	0.95 (–0.03 to 1.93)	0.29 (–0.01 to 0.59)
Fixed date vs variable date	173	45	8.50 (0.35) 9.01 (0.35)	–0.51 (–1.48 to 0.47)	–0.16 (–0.46 to 0.14)

SE, standard error.

TABLE 46 *Analysis of length of time to first peak anxiety score*

Comparison	Included in analysis	Missing	Hazard ratio (95% CI)
Rapid vs no Rapid test	191	27	1.62 (1.21 to 2.17)
Fixed date vs variable date	191	27	0.61 (0.45 to 0.83)

TABLE 47 *Number of adverse events by intervention factor*

Adverse events	Rapid test	No Rapid test	Fixed date	Variable date
n	107	111	112	106
Miscarriage	0 (0%)	1 (1%)	1 (1%)	0 (0%)
Lost sample	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Ruptured membrane leading to termination	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Hospitalised	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Abnormality on scan	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Total	3 (3%)	2 (2%)	2 (2%)	3 (3%)

TABLE 48 *Rapid versus no Rapid test women: comparison of analyses with all evaluable data compared with 159 with both datasets*

	Comparison	Included in analysis	Adjusted mean (SE)	Included in analysis	Adjusted mean (SE)
Primary end-point	Rapid test vs no Rapid test	181	11.05 (0.30) 13.29 (0.32)	159	8.66 (0.25) 10.54 (0.29)
1-month follow-up	Rapid test vs no Rapid test	173	9.23 (0.34) 8.28 (0.36)	159	9.20 (0.32) 8.23 (0.37)

SE, standard error.

One woman was hospitalised during the waiting period, had a normal karyotype result and completed her diary; she was included in the analysis.

An abnormality was found on the next scan of another woman; this woman had received a normal karyotype result, but did not return her diary.

Exploratory analysis

1-month follow-up

The results of the primary end-point, anxiety during the waiting period, indicate that Rapid test women are statistically significantly less anxious than no Rapid test women. Interestingly, the data at 1-month follow-up indicate that women recall their anxiety as it was, but their anxiety level at 1 month following receipt of a normal karyotype result indicates that no Rapid test women are considerably less anxious than Rapid test women. As this result is in the opposite direction to the primary end-point analysis, additional exploratory analysis was undertaken to investigate this interesting anomaly. This could, of course, simply be a chance finding.

The dataset used for the primary end-point analysis had 181 diaries that had sufficient data to be analysed, i.e. less than three consecutive days of data missing. The dataset for the 1-month follow-up analysis had 173 forms that were returned within the correct time frame and had complete data. Initially, it appeared that there were only eight women who were not in both datasets; however, only 159 women had complete data in the correct time frame for both analyses. *Table 48* summarises the primary end-point analysis (shown earlier) with the 181 diaries compared to a dataset with the 159 women that have both sets of data. The 1-month follow-up data are also summarised for both populations.

The tables indicate that the more anxious women have probably not completed the 1-month follow-up, that is, the adjusted mean for the primary end-point data for the Rapid test women reduces from

TABLE 49 *Fixed versus variable date: comparison of analyses with all evaluable data compared with 159 with both sets of data*

	Comparison	Included in analysis	Adjusted mean (SE)	Included in analysis	Adjusted mean (SE)
Primary end-point	Fixed date vs variable date	181	11.98 (0.30) 12.36 (0.32)	159	10.02 (026) 9.19 (0.27)
1-month follow-up	Fixed date vs variable date	173	8.50 (0.35) 9.01 (0.35)	159	8.55 (0.34) 8.88 (0.36)

SE, standard error.

TABLE 50 *Important covariates: are they predictive of anxiety at one month follow-up?*

	Included in analysis	Missing	Parameter estimate	Standard error	*p*-Value
Age at randomisation: <35 vs ≥35 years	173	2	–1.04	0.54	0.0573
Qualifications:					
None (1) 1 vs 3			0.98	0.93	0.2927
GCSE (2) 2 vs 3	172	3	0.70	0.56	0.2160
Post-16 (3)					
Maternal age: yes vs no	173	2	1.43	0.49	0.0044
Triple test risk: yes vs no	173	2	–1.14	0.50	0.0230
Parental anxiety: yes vs no	173	2	0.42	0.42	0.6570
Single soft marker for Down's syndrome: yes vs no	173	2	–0.43	1.12	0.7025
Previous problem: yes vs no	130	45	0.56	0.63	0.3755
Gestation (weeks)	173	2	–0.03	0.23	0.8964
Peak anxiety score during the waiting period	159	16	0.03	0.07	0.7049
STAI State baseline scores	173	2	0.01	0.02	0.5151

11.05 to 8.66 when the 22 women who do not have follow-up forms have been removed (however, the difference in anxiety is still in favour of Rapid test women). By removing the 14 women who did not have diary data from the 1-month follow-up analysis, the means remain approximately the same.

However, for the Rapid versus no Rapid test comparison the results still change direction, that is, for the primary end-point analysis no Rapid test women are more anxious but at 1-month follow-up this is reversed and Rapid test women are more anxious; even more interesting, the Rapid test women are actually more anxious at 1-month follow-up than during the waiting period.

Table 49 also indicates that the more anxious women did not complete follow-up forms; the table shows that the anxiety levels during the waiting period, that is, the primary end-point, are reduced when the 22 women not returning follow-up forms are removed from the dataset. Again, the adjusted mean for the 1-month follow-up data remains approximately the same. For this comparison, the direction of the change in anxiety remains the same.

An additional linear regression analysis was undertaken, adjusting for the intervention factors, the minimisation factors, the important covariates and the women's peak anxiety score during the waiting period to assess if any of these factors were predictive of anxiety score at 1-month follow-up.

Initially, each of the factors age at randomisation, education, reasons for amniocentesis (maternal age, triple test, single soft marker for Down's syndrome, parental anxiety), a previous problem which was defined as either a still birth/baby that died or a miscarriage or a previous baby with a serious abnormality, gestation, STAI State baseline scores and peak anxiety score during the waiting period were added into a model with the intervention factors. *Table 50* shows the

TABLE 51 *Age distribution for women having the amniocentesis for maternal age*

	Rapid test		No Rapid test		Fixed date		Variable date	
Maternal age	Yes	No	Yes	No	Yes	No	Yes	No
n	47	60	43	68	46	66	44	62
Mean (SD)	38.5 (2.5)	33.7 (4.9)	38.3 (2.8)	34.3 (3.5)	38.5 (2.5)	34.0 (4.3)	38.3 (2.8)	34.1 (4.2)
Median	38.7	34.6	37.9	34.5	38.6	34.3	38.0	34.9
Min., max	30.1, 43.4	18.2, 41.7	32.1, 43.3	21.3, 41.1	32.1, 43.3	21.3, 41.7	30.1, 43.4	18.2, 39.9

TABLE 52 *Age distribution for women having the amniocentesis for triple test risk*

	Rapid test		No Rapid test		Fixed date		Variable date	
Triple test	Yes	No	Yes	No	Yes	No	Yes	No
n	65	42	66	45	63	49	68	38
Mean (SD)	34.4 (5.2)	38.0 (2.6)	34.6 (3.4)	37.7 (3.7)	34.4 (4.3)	37.6 (3.5)	34.6 (4.4)	38.1 (2.7)
Median	35.3	38.0	34.8	37.9	34.3	37.9	35.4	37.9
Min., max.	18.2, 42.4	30.1, 43.4	27.7, 43.2	21.3, 43.3	22.5, 41.9	21.3, 43.3	18.2, 43.2	30.1, 43.4

significance level for each of these factors when added alone to a model containing the intervention factors. The table shows that maternal age as a reason for having the amniocentesis is the single most important predictor of anxiety levels at 1-month follow-up. Age at randomisation is also an important predictor of anxiety levels, but age at randomisation is confounded with maternal age and as it is less important than maternal age will not be included in any further analysis. Triple test as a reason for having an amniocentesis is also an important predictor of anxiety levels at 1-month follow-up. *Table 50* in baseline characteristics shows that only one woman gave maternal age and triple test result as reasons for having an amniocentesis, indicating that these two reasons are not confounded.

Continuous variables

An additional model containing both maternal age and triple test risk shows that maternal age is still important ($p = 0.0762$) after adjusting for triple test risk; however, triple test risk no longer remains significant ($p = 0.8570$).

A final model containing all the factors, after they have all been adjusted for each other, shows that maternal age remains significant at the 10% level ($p = 0.07$); interestingly the STAI State score becomes more important after adjusting for all other factors, but is not significant, $p = 0.1379$.

Table 51 summarises the age distribution for women having an amniocentesis for maternal age or triple test risk. As would have been expected, the results show that women having the amniocentesis because of maternal age are generally 4–5 years older; the mean age is very similar across the groups.

Table 52 shows that women having the amniocentesis for triple test risk reasons are generally younger; again, the mean age across the groups is very similar.

Plots

Figures 2–5 show the daily diary score, that is, the short form of the STAI as used in the analysis; the right-hand axis shows this as an equivalent score on the full Spielberger scale (this is simply the short form score divided by 6 and multiplied by 20). The plots show very nicely the differences between the intervention factors. The first two plots show the mean daily diary score and standard error bars for each of the diary days. The third and fourth plots show the mean daily diary score and standard error bars by number of days prior to receiving the karyotype result. Day 0 is at the right-hand side of the plot and is results day.

For comparison, women who learned they were carriers during stepwise prenatal screening for cystic fibrosis had a STAI mean score of 52;[33] screen negatives had a mean of 32.

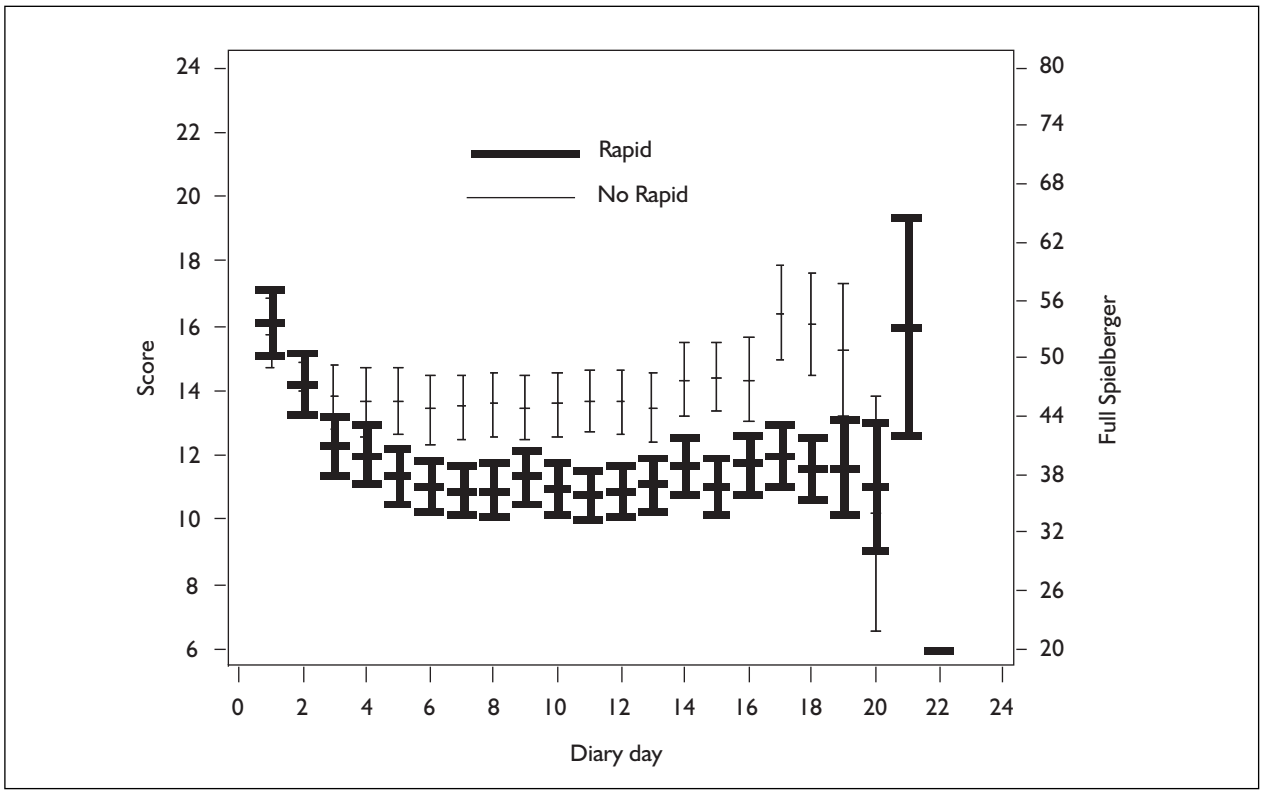

FIGURE 2 *Mean daily diary scores and standard errors for the Rapid versus no Rapid test patients*

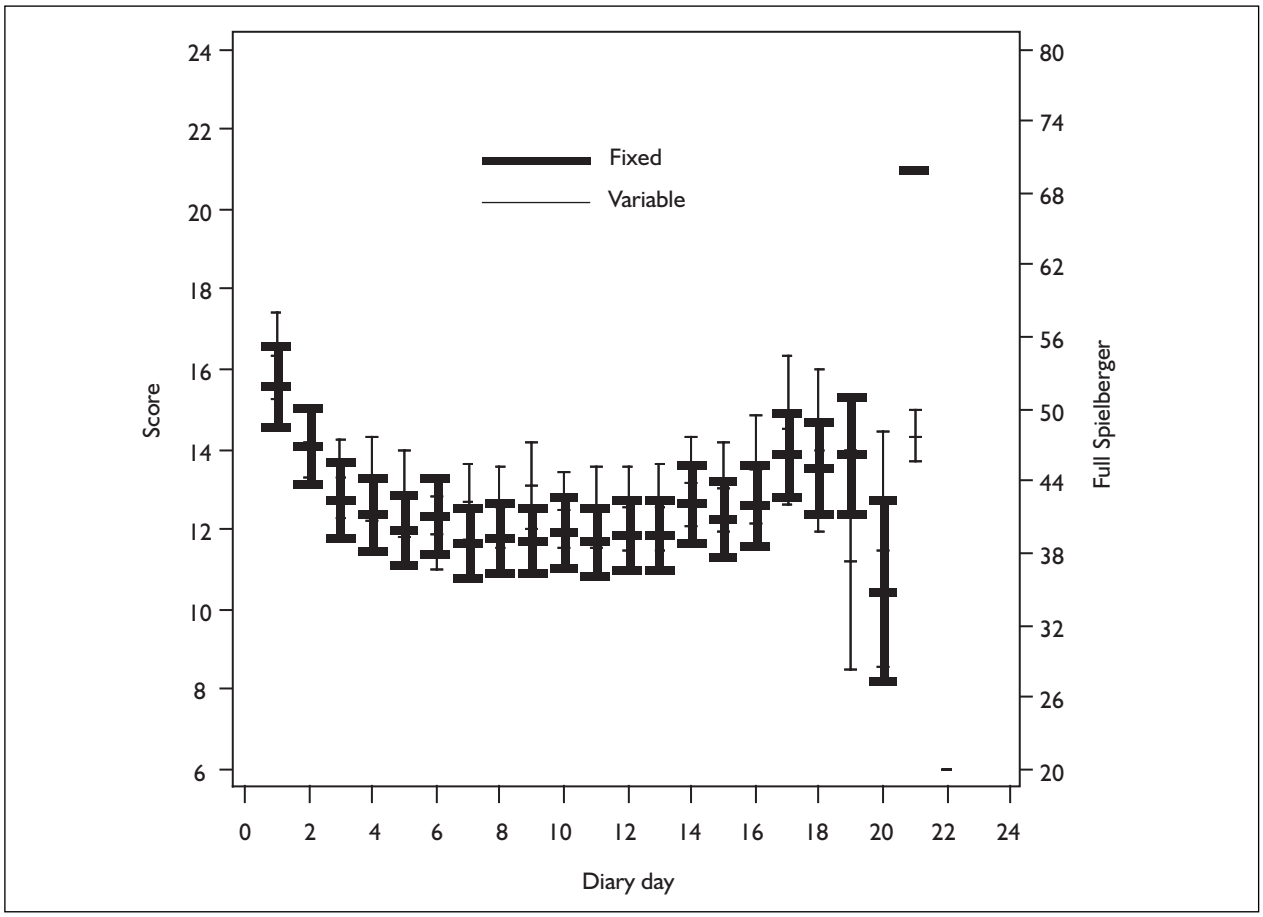

FIGURE 3 *Mean daily diary scores and standard errors for the fixed- versus variable-date patients*

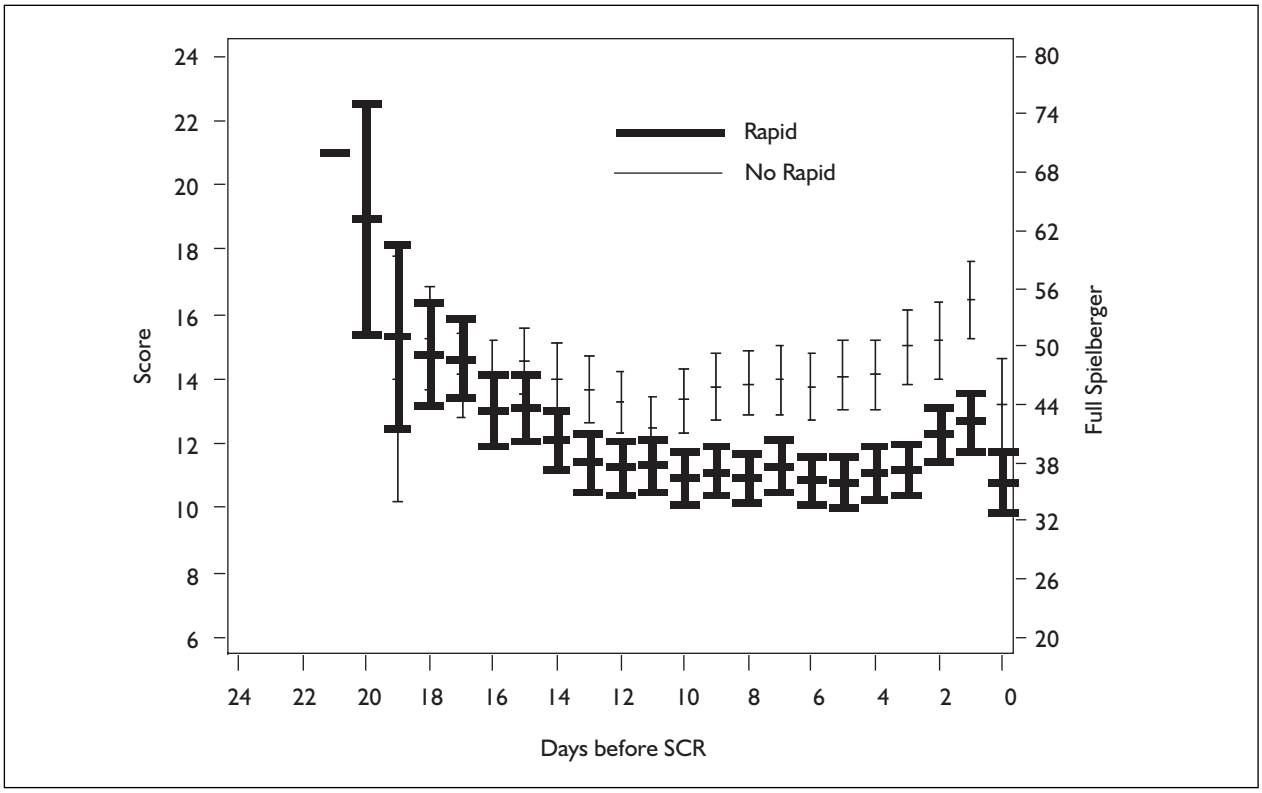

FIGURE 4 *Mean daily diary scores and standard errors by number of days prior to standard culture results (SCR) day for the Rapid versus no Rapid test patients*

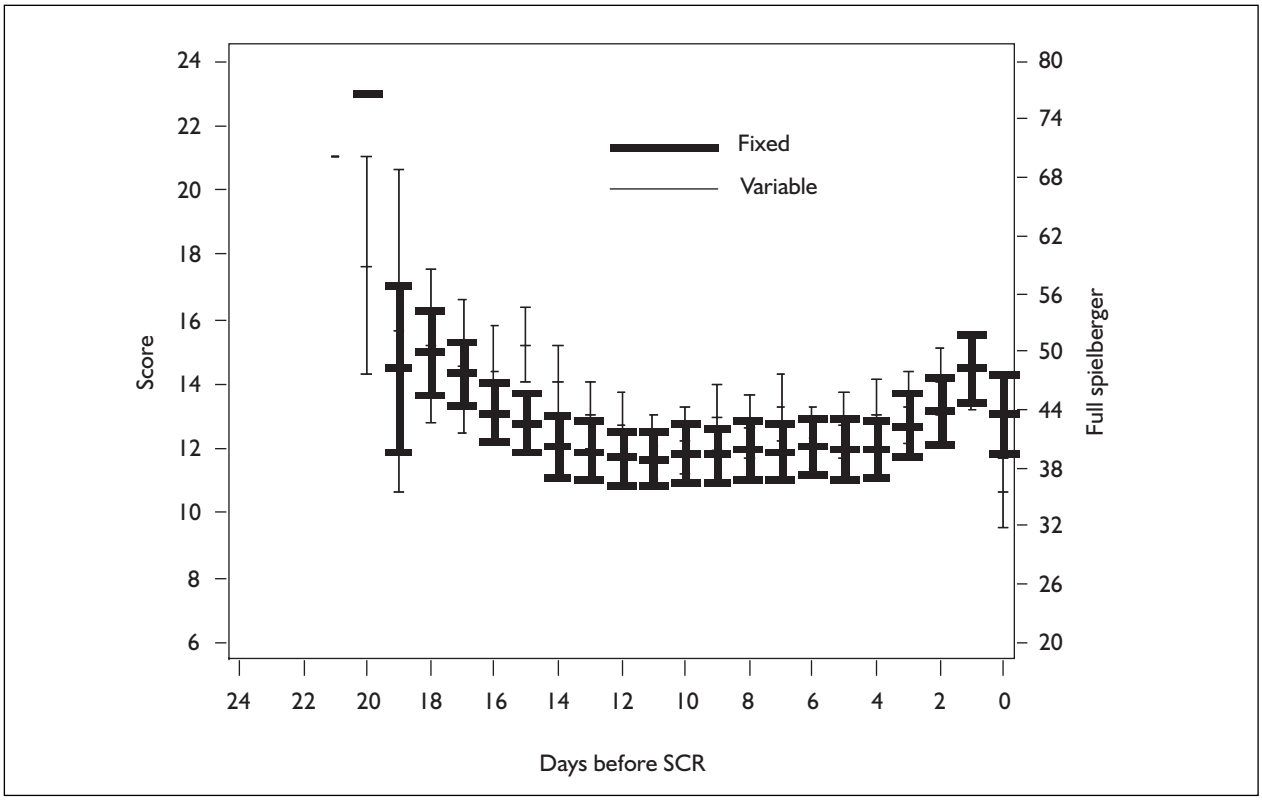

FIGURE 5 *Mean daily diary scores and standard errors by number of days prior to standard culture results (SCR) day for the fixed- versus variable-date patients*

Chapter 4
Discussion

Methodology

The study relied on a diary methodology to collect the required daily anxiety scores. This method proved acceptable to women, with a satisfactory proportion of diaries being completed to a usable standard. Follow-up 1 month after normal karyotype results was also acceptable to participants, although more anxious women were more likely to be lost to follow-up. The findings at follow-up were unaffected when this loss was taken into account.

Choice of primary end-point

Using a daily measure of anxiety, the SAUC from testing to results day was the chosen primary end-point for the trial. The adoption of this particular end-point was unproblematic for the comparison of Rapid and no Rapid testing, but the result of much deliberation for the fixed-date versus variable-date comparison.

It could be argued that using this end-point will bias the data towards a more favourable outcome for fixed-date participants, because variable-date women are likely to be more anxious for more days. However, the alternative of taking total anxiety over 21 days will bias the results in the opposite direction: variable-date participants receive their results earlier, so will spend more of the 21 days in the knowledge of their results and hence will be less anxious.

We considered that the most clinically meaningful end-point would relate to the waiting period, but agreed that the analysis of both the SAUC and the total anxiety over 21 days would test the robustness of the conclusions.

The ARIA project was commissioned in response to a perceived need for a better understanding of factors affecting women's anxiety while waiting for amniocentesis results. To maximise response rates, data collection instruments were kept as short as possible, and other possible outcomes such as women's preferences were not examined. The inter-relationship between measures such as anxiety and preference, and how this might change over time, is an important topic in its own right, but investigating it was beyond the scope of the present study.

Sample size and recruitment

The planned sample size was not achieved. This was mainly because of a reduction in the number of eligible women, but also in part because a smaller than expected proportion of women agreed to join the study. The overall number of women having an amniocentesis was lower than in the planning phase of the study, partly because the availability of first trimester nuchal translucency (NT) screening had caused a switch to CVS, and partly perhaps because of improved screening performance. After the study had begun, the introduction of Rapid testing on a private and eventually on an NHS service basis further reduced the numbers of women who were both eligible and willing to take part: of the 291 women who declined to participate, the stated reason in 168 cases (58%) was eligibility for an NHS Rapid test, and in a further 30 cases (10%) the woman was self-funding a Rapid test.

Anxiety experienced while waiting for karyotype results

One of the main arguments advanced in favour of rapid testing is that it will make women less anxious.[34] This study shows clearly that an anxiety reduction does occur after Rapid test results, and that it is substantial. The scale score difference in average daily anxiety was 2.24 (*Table 25*), which is equivalent to a (pro-rated) difference of 7.5 in full-form STAI values,[29] while the lower boundary of the 95% CI is equivalent to a difference of 4.6 full-form points. The magnitude of these differences may be interpreted by reference to known group comparisons:[24] the normative sample for the STAI had a mean score of about 34 and psychiatric patients a mean of about 48, a difference of 14 points. Even the lower boundary of the effect therefore represents a worthwhile and meaningful anxiety benefit from rapid testing.

The relative merits of releasing karyotype results as soon as they become available, or on a fixed

date, are less clear. No significant difference between these strategies was observed on the study's primary end-point, the average anxiety during the waiting period, but the achieved sample size was only large enough to permit moderate-to-large differences to be detected. It is possible, therefore, that one strategy does have a small advantage over the other in terms of the amount of anxiety experienced, but such a small effect would have few implications for clinical practice. It is also possible that there was an interaction between the study factors, with the effect of a fixed or variable date being reduced in women who had been given Rapid test results, but again, the study was not powered to detect such an effect.

These results were unaffected by taking into account demographic factors, medical history, the adequacy of the woman's social support and baseline measures of anxiety.

Analysis of the secondary end-points provided more detailed information about anxiety changes during the waiting period.

Peak anxiety was unaffected by either of the factors studied, but the time taken to reach the peak was shorter in women who had received Rapid test results and in women receiving their karyotype result on a variable date. These time differences are not themselves surprising, given the timing of the interventions, but they do contribute to validating the anxiety data obtained.

It was not expected that anxiety in the first 4 days after the amniocentesis would differ between groups, because all women would share similar concerns about the possibility of miscarriage, whether or not results had been received from Rapid testing. No group differences were found.

By 11 days post-procedure, it was expected that any benefit of Rapid testing should have become apparent. Women receiving karyotype results only would not have expected to receive their results by this time, but all women in the Rapid test group would have known for several days that the baby did not have Down's syndrome. The results fulfilled these expectations: there was no difference in anxiety over this period between women allocated to receive karyotype results on a fixed or on a variable day, but women who had received a Rapid test result experienced less anxiety over the 11 days than those who had not.

If the receipt of Rapid test results altered women's perceptions of the karyotype result, the effect would be noticeable between day 12 and results day. The average daily anxiety score over this period was found to be lower in women who had been given Rapid test results.

It was reasoned that anxiety differences between strategies of giving karyotype results on fixed or variable dates should also have become apparent between day 12 and karyotype results day. The average daily anxiety score over this period was found to be very similar in the fixed- and variable-date groups.

It should be noted that the SAUC for this period is potentially vulnerable in the fixed-date versus variable-date comparison, because – as explained above with reference to the primary end-point – it is an average over days and does not reflect the number of days contributing to that average. In most cases, participants allocated to the variable-date group waited a shorter time for their result. Robust conclusions cannot therefore be drawn about this factor on the basis of these data.

Total anxiety to day 21, when all results had been issued, was less if women had received a rapid test. There was no evidence that issuing karyotype results on a fixed or variable date made a difference to the overall anxiety experienced. As noted at the beginning of the chapter, this end-point is potentially biased in the opposite direction to the primary end-point, so the consistency of the findings suggests the main conclusions are robust.

Comparing anxiety levels in the 7 days prior to karyotype results day also raises some problems of interpretation for the fixed-date versus variable-date comparison, because the fixed-date group knew when results day would occur, but the variable-date group did not. Once again, however, the results are consistent with those of the other analyses: anxiety was lower in people receiving a Rapid test, but it was very similar in women receiving karyotype results on fixed and on variable days.

Recalled anxiety

When women were asked to remember the anxiety they had experienced during the 10–12 days following the amniocentesis, no group differences were found. However, when asked about the 2–3 days prior to receiving the karyotype result, women who had had Rapid testing recalled their anxiety as having been lower. The diary data showed that women who had received Rapid test results were less anxious over both the earlier

period and the later period. Recalled anxiety for both periods was very similar in women who had received their karyotype results on a fixed or on a variable date, which corresponded to the diary evidence.

Anxiety 1 month after karyotype results

Anxiety 1 month after karyotype results showed a different pattern. Overall, anxiety was low at this time, but there was a small to moderate increase in anxiety in women who had received Rapid test results compared with those who had only received the results of karyotyping. This pattern persisted after adjusting for loss to follow-up and for important covariates. There was no evidence of difference on the fixed-date versus variable-date comparison.

Exploratory analyses

Women for whom maternal age was the main reason for having an amniocentesis were more anxious 1 month after normal karyotype results than women tested for other reasons. Anxiety at baseline was an important predictor of anxiety while waiting for karyotype results, but was not a predictor of anxiety at follow-up.

Comparison with other studies

The earlier UK study[25] of the effect of rapid testing on anxiety also included a 1-month follow-up. Both studies used the short form of the STAI to measure anxiety, but when reporting their results, Grimshaw and colleagues[25] converted short-form to full-form STAI values, using the recommended[29] simple pro-rating based on the numbers of items (six items in the short form, 20 in the original STAI State Anxiety scale). When a similar conversion was carried out on the present study data, women in the two studies showed very similar levels of anxiety at baseline, with mean scores of about 47–49 (data points for Grimshaw and colleagues[25] are estimated from Figure 17, on page 76 of their report).

After receiving a Rapid test result, women in the earlier study had a mean score of 39; from inspection of *Figure 2*, the equivalent mean in the present study was about 40. Four weeks after receiving karyotype results, mean scores were 35 (Rapid) and 34 in the earlier study and 31 (Rapid) and 28 in the present study. Unlike the present study, the earlier one did not use individual randomisation: in one of the study areas, all women were entered into the intervention arm of the study (i.e. they were offered a molecular test) and in the other area, control participants were recruited after a period in which all women were offered the intervention. The experience of women in both studies differed from routine practice in that they filled in a number of anxiety questionnaires, which may have made them more aware of their anxiety, but in other respects, being in a research project would have had little impact upon them. In the present study, the trial midwife had a brief telephone conversation with participants, which included the issuing of test results as appropriate, but the study recruited from a large geographical area and all other care was provided by local staff in the usual way. In these circumstances, and given the close similarity in the results of the two studies, it seems reasonable to conclude that the results of the present study are likely to be generalisable outside of the trial context. It must be acknowledged, however, that anxiety patterns in women unable to complete self-report questionnaires in English have not been adequately studied to date. Generalisation to other testing regimes would not be justified: anxiety in women who are only offered Rapid testing has not been studied and may take a different course.

There is no ready explanation for the raised anxiety seen in the Rapid test group at the 1-month follow-up. Anxiety theorists have argued for some time[22] that reassurance can have paradoxical effects, but mechanisms of action are poorly understood. One possibility is that brief reassurance does not address the fundamental root of anxiety but does have a transient effect on current emotion; the transient effect is soon dissipated, and anxiety increases, leading to the wish – and perhaps ultimately the need – for more and yet more reassurance. Another possible mechanism might be that receiving two lots of test results, answering slightly different questions, implies that no test is definitive and that further tests might yield yet further information. Residual anxiety in 'false positives' following prenatal testing is now well documented.[6] In the era of increasing numbers of tests and different kinds of tests, the psychological effects of giving one set of results after another need to be better understood than they are at present.

In addition to collecting information about anxiety, Grimshaw and colleagues[25] studied the preferences of 141 women in their study who had been allocated to receive Rapid testing in addition to karyotyping. When asked before amniocentesis which test they would have if they had to choose,

67% opted for Rapid testing and 32% for karyotyping; after all results were known, the figures were 52% and 43%, respectively. These results show how much preferences can differ between individuals, and suggest also that preferences can change with circumstances. Ryan and colleagues[35] reported results from discrete choice experiments conducted with 49 pregnant women, but only 10 of these were actually having an amniocentesis, the remainder attending just a routine 11-week scan. They concluded, on the basis of aggregate results, that women prefer simple to comprehensive information provided that the former is available 6 days sooner than the latter. However, as it seems likely that preferences will differ between the two subgroups, this conclusion must be treated with caution until more data are available.

Policy implications

The present study has shown that rapid testing is a beneficial **addition** to karyotyping, reducing women's anxiety while they are waiting for karyotype results. Since screening programmes should do more good than harm, and since the period of waiting is known to be a very anxious time, the policy implications of this finding must be addressed; however, this is not as straightforward as it might at first appear. First, adding a new test to an existing programme has obvious cost implications. Second, the anxiety benefits from Rapid testing are short-lived: 4 weeks after karyotype results, they have gone, which raises questions about value for money.

Third, there are unanswered questions about whether any longer term effects might be negative rather than positive. Important as these points are, the study's policy implications are much more limited by a change in the policy debate that has taken place since the study began: Rapid testing has been proposed not as an addition but as a **substitute** for karyotyping, a change which has strong economic attractions for policy makers. Given this policy context, it must be stressed that the findings of the present study – even the most positive ones – cannot be interpreted as supporting a strategy of substitution, because the effects of that strategy were not examined.

Although there are limitations to the study's direct policy implications, some indirect ones deserve brief consideration. The studies of women's preferences[25,35] have shown no clear consensus in favour of early information over comprehensive information, because both are valued. Issuing a single set of results from an early, comprehensive test must therefore remain the goal. Until then, it is reasonable to ask – temporarily leaving aside economic considerations – if a combination of tests (here a Rapid test and a comprehensive test) will produce a combination of benefits. The findings of the present study suggest that this may not be the case, because there may be psychological disadvantages to having two sets of results rather than one. The more general point is that the psychological effects of changing a testing regime may not be straightforward, and claims of benefit – or indeed, assumptions about lack of harm – should be treated with caution in the absence of supportive evidence.

Chapter 5
Conclusions

We found no evidence that giving amniocentesis results out on a planned date (fixed date) with an undertaking not to telephone earlier, even if possible, alters maternal anxiety during the waiting period, compared with a policy of telling women that the result will be issued as soon as available (variable date). These results are not conclusive, however, as the analysis only had sufficient power to detect a moderate to large effect.

We found that the issuing of early results from a partial but rapid analysis (Rapid test) reduces maternal anxiety during the waiting period, compared with receiving only the full karyotype analysis (no Rapid test).

The above conclusions relate to the study's two main aims. We found in addition that group differences in recalled anxiety reflected fairly closely the differences in anxiety experienced while waiting for results.

One month after receiving normal karyotype results, we found that anxiety was low in all groups, but that women who had been given Rapid test results were more anxious than those who had not.

Implications for healthcare

Since there are no clear advantages in anxiety terms of issuing karyotype results as soon as they become available, or on a fixed date, both practices may be considered to be acceptable and women should whenever possible be able to choose the method that is best for them.

Rapid testing is a beneficial addition to karyotyping, reducing anxiety to normal levels, at least in the short term.

The above finding does not necessarily imply that early results would be preferred to comprehensive ones if women had to choose between them. There are powerful economic arguments for replacing karyotyping with Rapid testing, particularly with PCR,[25,36] and this has already happened in some parts of the country. Others have urged caution, arguing that women's preferences must be taken into account before making such a major policy change.[37–39] Only limited information on women's preferences, and the factors that influence them, is at present available.

Recommendations for future research

There is no need for more studies of the effect on anxiety during the waiting period of adding Rapid testing to conventional karyotyping. There remains a need for longer term studies of other testing regimes:

1. There should be further research, including more qualitative studies, into the causes, characteristics and consequences of anxiety associated with prenatal testing in women of differing ages and backgrounds.
2. The effects of different testing regimes on short- and longer term anxiety, on the preferences of women and on the relationship between anxiety and preference should be investigated in women of differing ages and backgrounds.
3. More research is needed on the effectiveness and cost-effectiveness of methods to minimise anxiety in different testing regimes.
4. Further research is required into the policy implications of incorporating individual preferences for different testing regimes into prenatal testing programmes.

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The ARIA Trial Group:

1. Trial Management Group (Appendix 6)
2. Members of the Trial Steering Committee (Appendix 5)
3. Independent Interim Analysis Committee (Appendix 7)
4. Midwifery and Obstetric/Fetal Medicine Coordinators:
5. Additional Clinical Trials Research Unit staff:
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Contribution of authors

Jenny Hewison (Professor of the Psychology of Health Care) was joint chief investigator, and contributed to the conception, design, conduct and monitoring of the trial and to the analysis and writing of the report. Jane Nixon (Deputy Head of the Clinical Trials and Research Unit) contributed to the design, conduct and monitoring of the trial and to the analysis and writing of the report. Jayne Fountain (Senior Medical Statistician), trial statistician, contributed to the design, conduct and monitoring of the trial, undertook the analysis and contributed to the writing of the report. Kim Cocks [Assistant Director (Statistics)], supervising statistician, contributed to the design, conduct and monitoring of the trial, supervised the analysis and contributed to the writing of the report. Clare Jones (Research Midwife) contributed to the literature review, protocol development and implementation, interpretation of the results and the writing of the report. Gerald Mason (Consultant in Feto-maternal Medicine) contributed to protocol development and implementation, interpretation of the results and the writing of the report. Stephen Morley (Professor of Clinical Psychology) contributed to the conception, design, conduct and monitoring of the trial, interpretation of the results and the writing of the report. Jim Thornton (Professor of Obstetrics and Gynaecology) was joint chief investigator and contributed to the conception, design, conduct and monitoring of the trial and to the analysis and writing of the report.

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Appendix 1
Original proposal

Planned investigation

Background

Doctors often have to issue important test results, such as tumour biopsy results, pregnancy tests after *in vitro* fertilisation and serum-screening results, days after the test was performed. Patients, especially those increasing numbers who wish to be fully involved in their healthcare decisions, often find find the waiting period a time of anxiety. The results of amniocentesis tests are particularly problematic because the delay may be up to 4 weeks and the normality of a wanted pregnancy often hinges on the result. High anxiety while waiting for the results is common although not invariable,[1–5] and there is a need to try to minimise this anxiety. Parents also experience many other emotions such as anger and guilt at this time.[6,7] Although recent developments such as chorionic villus sampling (CVS), techniques for culturing cells directly on examination slides and fluorescence *in situ* hybridisation (FISH), may reduce the waiting period, these are unlikely to become universal in the foreseeable future. CVS has higher procedure-related miscarriage risks, slide culture is expensive and labour intensive and FISH detects only two-thirds of important chromosome abnormalities.[8,9] Delays of up to 3 weeks are likely to remain for some time, justifying the need to investigate methods of reducing anxiety during this period.

Patients awaiting results of screening tests, such as triple tests, may also feel anxious. However, we feel that these should be the subject of separate study. Patients undergoing screening typically worry relatively little about the test during the waiting period (which in the case of the triple test is only approximately 7 days), because even if the test is positive they will usually only have a small risk of an affected pregnancy. In contrast, patients undergoing a diagnostic test face the reality of a Down's-affected pregnancy at the end of the waiting period.

From clinical experience, anxiety about amniocenteses occurs in three phases, each related to different concerns. Prior to the test women worry whether to undergo it, immediately post-test they worry whether the test caused harm and finally just before the result concerns are centred on the outcome of the result. Anxiety surrounding the first phase has been reasonably well researched, but the other phases have been relatively neglected. It is broadly established that anxiety levels return to normal after the test result has been communicated,[3,6,7,10] but little is known about the period just prior to the receipt of the result. There is considerable variation, and at least one small-scale study (n = 37) has reported that "unexpected anxiety levels were low over the last few days before the diagnostic results became available".[11] The focus of the current study is on anxiety while waiting for, and receiving, test results. The main objective of the study is to test whether a simple, easily implemented, theoretically derived, intervention can modulate anxiety felt in anticipation of the receipt of the test result. In addition, the study will provide more detailed information on the course of anxiety over the whole period after the amniocentesis procedure.

Anxiety arises when a person perceives that a valued goal is threatened and the magnitude is proportional to the importance of the goal.[12] Women undergoing amniocentesis fit this rule. For example, Marteau *et al*.[13] found that anxiety was associated with the perceived risk of having an abnormal baby, that is, the degree to which their goal of having a healthy baby was threatened. Once aroused, a range of factors influence anxiety and in order to establish the key determinants of anxiety following amniocentesis we will consider four types of factors: situational, coping, personality and social.

- *Situational*: The degree to which a threat is predictable is a major influence of anxiety. Ambiguity about the imminence of a threat is associated with greater anxiety.[12,14,15] Knowledge of when and where a threatening event will occur generally confines the experience of anxiety of a smaller anticipatory 'window'. Under these circumstances, the peak magnitude of anxiety (normally experienced just prior to the event) may not be reduced, but the total anxiety experienced up to that point is truncated. Present practice in the centres involved in this study is to inform women that

their results will be available as soon as the test is complete, normally between 14 and 21 days. This is an implicit attempt to reassure women that the service will work as fast as possible, but may be counter-productive because of its inherent unpredictability.
- *Coping*: This describes how people appraise and evaluate threatening information and the cognitive, behavioural and emotional control processes instituted to minimise the impact of a threatening event. Although it is possible to teach people desirable coping strategies, even a brief intervention would be labour intensive and difficult to transfer to other settings. We believe such interventions are best reserved for more extreme cases of anxiety. Our proposal is to develop a leaflet to inform women of the experience they are likely to undergo while waiting for the result. The content will be devised from information obtained in the initial observational cohort study. Such normative information about the issues that generate anxiety should reduce worry about worry. The principle behind this approach to coping is derived from Leventhal's general model of emotion and coping, and the associated observations in many studies on preparation for a variety of medical procedures.[16–18] These have shown that provision of information about procedures reduces emotional arousal.

The remaining two influences on anxiety are difficult to manipulate but will be measured to assess their influence on the impact of the intervention.

- *Personality*: 'Personality' is a relatively stable source of variance between people which has behavioural affective and cognitive components. Several personality traits are associated with coping with experience of anxiety.[19] We propose to assess a cognitive style (monitoring versus blunting). Monitoring refers to the extent to which people pay attention to threat-relevant information and blunting to how they avoid emotionally arousing information. Monitoring/blunting (MB) is a robust phenomenon.[20] Monitors show a greater need for medical and stress-related information than blunters and appear to value certainty over the exercise of control. There is an interaction between the monitoring and blunting personality and the content and provision of information[21,22] with several studies in the area of women's health.[23,24]
- *Social*: Pregnancy and childbirth are inherently social, with partners and immediate family members, particularly the woman's mother, advising and providing support. Relatively little quantitative information is available on the factors that influence this. We propose to examine the impact of such support using the modified Significant Other Scale[25] to assess support from the partner, mother and closest woman friend.

Plan of investigation

Centres performing over 40 amniocenteses annually will be involved. Participants will have undergone an amniocentesis test because of maternal age, triple test risk or soft marker for Down's syndrome.

The study will comprise two phases. Phase I will be an observational cohort study to explore the feasibility of daily anxiety assessments in a randomised trial and to identify the factors associated with anxiety, to be assessed in the trial. Phase II will be a randomised controlled trial to assess the impact of providing women with a fixed date for receiving test results, as opposed to providing them when available. The trial will also evaluate the impact of a debriefing leaflet on anxiety levels.

In Phase I, women will complete a daily anxiety diary and will be given their results when available. They will then be interviewed by the Research Midwife to explore factors associated with anxiety, recall of anxiety, comments made on the diary card and levels of social support.

In Phase II, participants will be randomised immediately after the amniocentesis procedure to 'phone result when available' or 'issue result on a fixed date' and to 'leaflet' or 'no leaflet'. Daily assessments of anxiety will be recorded.

Aims

Phase I

The aims of Phase I, the observational cohort study, are to:

- assess the feasibility of and compliance with 3 weeks of daily assessments of anxiety
- improve the design and layout of the daily diary (if necessary), to maximise compliance in the trial
- identify determinants of anxiety to be assessed in the trial, for example the role of social support
- identify the important end-points for participants (peak anxiety, overall level of anxiety, number of days with anxiety, etc.)
- identify information to be incorporated into the trial leaflet.

Phase II

The aim of Phase II, the randomised controlled trial, is to test the following hypotheses:

- That giving amniocentesis results out on a fixed date, with an undertaking not to telephone earlier even if possible, alters maternal anxiety during the waiting period, compared with a policy of telling parents that the result will be issued 'when available'.
- That providing participants with a 'debriefing' leaflet, describing the normal pattern of worry during the waiting period, changes anxiety levels.

Design

Phase I will be an observational cohort study. Phase II will be a multi-centre 2 × 2 factorial design open randomised controlled trial.

Eligibility criteria

The following eligibility criteria apply to both phases of the study.

Inclusion criteria

1. Women who are pregnant.
2. Gestation $14^{+\ 0\ \text{days}}$–$20^{+\ 6\ \text{days}}$ weeks.
3. Women aged at least 16 years.
4. Single foetus.
5. Women undergoing amniocentesis for the following primary indications:
   (a) Maternal age alone (women may be included at any age provided it is sufficient to make them wish amniocentesis).
   (b) Triple test risk (women may be included at any risk provided the risk is sufficient to make them wish amniocentesis).
   (c) Single soft marker for Down's syndrome. This includes the presence of abnormal nuchal translucency, a short femur or a dilated renal pelvis, provided that in combination with maternal age this was felt sufficient to indicate amniocentesis.
6. Women able to read and complete the daily anxiety assessment.
7. Women who have given written informed consent.

Exclusion criteria

1. Amniocentesis performed primarily to diagnose a single gene disorder, neural tube defect or for rhesus disease.
2. The presence of a major structural abnormality detected on ultrasound.
3. Either parent carrying a balanced translocation.

Registration/randomisation

Phase I

Registration into the observational cohort study will take place immediately after the amniocentesis by a telephone call to the Northern and Yorkshire Clinical Trials and Research Unit's (NYCTRU) automated 24-hour registration/randomisation service. After confirmation of eligibility, a study number will be assigned.

Phase II

Randomisation into the trial will take place immediately after the amniocentesis test by a telephone call to the NYCTRU's automated 24-hour registration/randomisation service. After confirmation of eligibility, a trial number will be assigned. Participants will be randomised to 'telephone result when available' or 'issue result on a fixed date' and to 'leaflet' or 'no leaflet'. The trial will be stratified by centre and maternal age (<35, ≥35 years).

Assessments/data collection

The following data will be collected for all participants in both phases of the study.

Pre-registration/randomisation

The Research Midwife will collect the following information prior to registration/randomisation:

- patient details (name, date of birth, hospital number, socio demographics)
- hospital
- name of consultant
- confirmation of eligibility
- date of test
- parity
- route to amniocentesis test
- trait anxiety [assessed by State–Trait Anxiety Inventory (STAR)[26]]
- depression [assessed by Centre for Epidemiologic Studies Depression (CES-D) Scale[27]]
- coping style (assessed by the Miller Behavioural Style Scale)
- level of social support (assessed by a modified Significant Others Scale[25]).

Post-registration/randomisation

Participants will be required to complete a daily diary card comprising the six-item short form of the Spielberger STAI[28] for 3 weeks from the delay of registration/randomisation. Data will be collected for 3 weeks to ensure that all patients have received their results at the end of completion (5% of results will not be available by day 18), and also to avoid any focus on day 18.

The card will provide the patient with space for additional comments.

The Research Midwife will conduct a post-test assessment with all participants. In Phase I, this will comprise a face-to-face interview with the patient at home. This will be tape-recorded and content analysis performed to develop the debriefing leaflet for the randomised trial, and to ensure that the most relevant anxiety-associated factors are assessed by the questionnaires. The women's recall of their anxiety on the days prior to the test results will also be evaluated. In Phase II, a retrospective assessment will be made using a mixture of open- and close-ended questions about anxiety during the waiting period, levels of support and the participant's preferred waiting time (fixed or unfixed). This will be carried out via a telephone call to the participants after the test results have been given.

Interventions

In the participating centres, standard practice is to issue results by telephone. Most doctors believe that this is the only practicable method. A letter is inappropriate as it adds an extra time delay, it is difficult to ensure that the message has been received and parents often have extra questions, such as the sex of child. A face-to-face consultation is impracticable for women who live far away or who work, especially since partners often wish to be present as well. We do not therefore propose to evaluate postal or face-to-face communication. Hence all amniocentesis results will be issued by a telephone call to the woman by the study Research Midwife.

In Phase I, all women will be given the results of the test when available. In Phase II participants will either be given the results when available or on day 18, depending on the randomised allocation. Participants randomised to be 'issued the results when available' will be told that the midwife will ring them with the result as soon as it is available, which is usually between 2 and 3 weeks after the test. Participants randomised to be 'issued the results on day 18' will be told that 95% of results are available by day 18 and that they will be phoned on that day. A fixed time will be agreed. Participants in this group will be given abnormal results immediately despite the 18-day plan. However, they will not be told this in advance unless they ask directly. Participants randomised to receive the debriefing leaflet will be given the leaflet after randomisation and will be able to take the leaflet home.

End-points

Primary end-points

Peak anxiety

Peak anxiety in the period between having the amniocentesis test and receiving the results, as measured by a daily score on the six-item short-form State Scale of the Spielberger STAI.

Total anxiety in the 11 days following amniocentesis

The period of high risk of miscarriage is the first 10 days. It is hypothesised that if the leaflet is going to have an effect on anxiety levels immediately following amniocentesis and during the period of high risk of miscarriage, this effect should be maximised in the time up to 11 days post-amniocentesis.

Total anxiety between days 12 and 21 inclusive

It is hypothesised that both the leaflet and telephone intervention will impact on the anxiety leading up to receiving the amniocentesis test result. All women will be asked to complete daily diaries for 21 days to allow fair comparison of total anxiety throughout this period.

Secondary end-point

Recalled anxiety, measured 1 month after receiving the amniocentesis

Patients will be asked to recall the anxiety they felt in the few days before receiving their amniocentesis test result. A simple numerical scale will be used, which will be piloted in Phase I of the study. It is likely that the issue of anxiety while waiting for and receiving antenatal test results has been raised through women's retrospective recall. This measure is an attempt to link women's perception of what they recall the experience was like for them, with the primary end-points.

Statistical considerations

Sample size

A total of 30 women are required to explore the feasibility of the daily assessment, to identify determinants of anxiety to be assessed in the randomised trial and to look at ways of asking about recalled anxiety. The information gathered will also be used to design the debriefing leaflet for use in the trial. The observational cohort study will also provide more information on the take-up rate for the study and, if necessary, to ensure sufficient randomisations in the proposed trial, the number of centres included in the study will be reviewed.

There is no theoretical reason to anticipate an interaction between the two main effects of leaflet

and phoning. We assume that the score on the six-item short-form of the State Scale of the Spielberger STAI is normally distributed in the target population.[28] In order to detect a moderate effect size of 0.3 SD, for either main effect (for any of the primary or secondary end-points) with 80% power at the 5% significance level (two-sided test), a total of 390 women would be required to be randomised in Phase II (allowing for a drop-out/non-compliance rate of 10%).

Patient accrual

The total number of amniocentesis tests performed at each of the participating centres is 600 per year, resulting in a pool of 900 potential participants in 18 months. If 45% of women were eligible and gave informed consent, which should be achievable with the provision of Research Midwife time in each centre, then 390 participants could be recruited in 18 months. It is estimated that 30 women could be recruited for Phase I in 3 months.

Statistical analysis

No formal statistical analyses will be made for the observational cohort study. Compliance with the daily diary cards, calculated as number of days fully completed divided by 21, will be calculated.

In the randomised trial, a regression approach will be used for the analysis of all end-points for both interventions. For each intervention, end-points will be reported as adjusted mean differences, where the adjustment will be for the other intervention and the randomisation stratification variables, age and centre.[29] p-Values less than 0.05 will be considered to be statistically significant. No adjustments will be made for multiple comparisons.[30] Adjusted mean differences with 95% confidence intervals will also be reported.

The sample size calculation is based on a t-test comparison of the difference in the means of two groups. A regression approach may reduce the estimate of the standard deviation of the effect and hence provide a more precise estimate of the effect of the intervention.

Formal hypothesis testing will be restricted to the primary end-points. All other hypothesis testing will be informal and interpreted as such.

Women who receive a positive test result will be excluded from analysis. Missing diary data will be examined carefully and appropriate methods for imputing missing data used if necessary. All analyses will follow a detailed prespecified analysis plan. The following outlines the planned analyses for the main outcomes.

Primary end-points

- The adjusted mean difference in peak anxiety between the two arms of each intervention separately
- the adjusted mean difference in total anxiety from days 12 to 21 inclusive, between the two arms of each intervention separately
- the adjusted mean difference in the total anxiety in the 11 days following the amniocentesis, for the leaflet intervention only.

Secondary end-point

- The adjusted mean difference in recalled anxiety, measured 1 month after receiving the amniocentesis.

Exploratory analyses

Regression analyses will be performed to explore the differences between arms of the interventions for the primary end-points adjusted for baseline scores on the CES-D Scale, the STAI Trait Scale and the Miller Behavioural Style Scale, together with other covariate information collected at baseline and a measure of social support (adapted from the Significant Others Scale). For each intervention these analyses will also include the other intervention and the randomisation stratification variables, age and centre. It is anticipated that these analyses will help to describe the variation observed in the data.

Predefined subgroups

The effect of each intervention will be explored within coping styles subgroups (determined by the Miller Behavioural Style Scale) by fitting an interaction term in a regression analysis. It is recognised that there will be limited power for this comparison.

Trial monitoring

A Trial Steering Committee will be established to provide overall supervision of the trial, in particular trial progress, compliance of daily assessments, adherence to the protocol and consideration of new information. An independent Chair will be appointed and all applicants will be members. The Committee will meet at least 6-monthly.

Recruitment will be monitored by the NYCTRU and the Trial Steering Committee. Data management and analysis will be performed by staff at the NYCTRU in accordance with the Unit's standard operating procedures based on MRC Good Clinical Practice Guidelines.

Ethics

The NYCTRU will ensure that the trial receives MREC approval and then LREC approval from each centre and that written informed consent is obtained prior to registration and randomisation. Participants will be free to withdraw from the trial at any time without giving reasons:

Project milestones

- **Pregnant activation** — Obtain ethical approval from MREC
- 0–2 months: Obtain ethical approval from LRECs
  Appoint research midwife
  Set up observational cohort study
- 3–8 months: Conduct observational cohort study with 30 women
- 9–12 months: Analyse and write up observational cohort study
  Prepare debriefing leaflet for the randomised trial
  Set up randomised controlled trial
  Produce protocol, diary card and data collection forms
  Launch meeting
- 12–30 months: Randomisation of 390 participants
  Data collected for all randomised participants
- 31 months: Follow-up of randomised participants
- 32–36 months: Analysis and publication of results.

Expertise

This group is ideally placed to perform this study. Jim Thornton has considerable experience in conducting clinical trials including a trial of different methods of information giving in this area,[31] and has just completed a small pilot trial of decision analysis for the amniocentesis decision.[32] Jenny Hewison provided the expertise in psychology for both trials. Stephen Morley is a psychologist with experience of outcome measures in clinical trials. Gerald Mason is Clinical Director for Obstetrics and Foetal Medicine and performs approximately 30% of all invasive procedures for the region. He holds a deep interest in the psychological problems caused by false-positive ultrasound results.

The NYCTRU has a comprehensive statistical, programming and trial coordination expertise and is running over 30 multi-centre clinical trials and research projects at national and international level. The Unit has particular expertise in trials in the reproductive field and in measuring psychological outcomes of trials by questionnaire. Mrs Julia Brown is joint head of the unit and has considerable statistical and trial expertise.
Ms Vicky Ryan will be the trial statistician, and also has considerable statistical and trial expertise. Mrs Maxine Stead has extensive trial coordination and quality of life expertise, including qualitative methodology, and will provide trial management support. The NYCTRU will design the data collection forms and patient information leaflets, produce the protocol, assist in the applications to MREC and LREC, coordinate the study on a day-to-day basis, register and randomise participants, manage the data, publicise the trial, prepare interim reports for the Trial Steering Committee, analyse the results and assist in writing papers for publication. The staff will liaise closely with the Research Midwives to ensure optimal recruitment and timely and accurate data collection.

The group of participating hospitals and clinicians involved all have excellent track record in recruitment to clinical trials, both locally organised ones (Home BP and GRIT) and in other national trials (Term Breech, ORACLE, Magpie).

Justification of the support required

A full-time Research Midwife is required to recruit women and conduct the interviews in Phase I, telephone all participants with test results in both phases, analyse the Phase I data, assist in the design and preparation of the debriefing leaflet, conduct the assessments in Phase II, train and support the centre midwives and assist in data collection and in the interpretation and publication of the results. The Research Midwife will hold a workshop for all centre midwives prior to the start of the study to ensure that the team is well informed about the study objectives and plans. This workshop will be repeated at 6-monthly intervals to ensure a good team spirit, resolve problems and maintain recruitment. This strategy has been used to good effect in other recent midwife-led trials (Oracle/Team Breech).

One hour per week of a midwife's time in each centre is necessary to ensure maximum recruitment, to ensure that participants are fully

informed about the trial and briefed about the daily assessments and to collect all clinical data and baseline quality-of-life assessments.

The budget for the NYCTRU is to support a dedicated project team working on MRC Good Clinical Practice Guidelines (senior statistician, senior trial coordinator, computer programmer) involved in the design, set-up, coordination and analysis of the trial, production of all trial material (protocols, forms, patient information sheets, publicity material, stationery), travel to centres, launch meeting and Trial Steering Committee expenses.

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Appendix 2

Patient consent form

(Form to be on hospital headed paper)

Version 1, January 2002

Study Number:

PATIENT CONSENT FORM

Title of Project: ARIA Trial – Investigating maternal anxiety experienced when awaiting amniocentesis results

1. I confirm that I have read, understand and have been given a copy of the information sheet dated ..... (version .....) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the research staff or from regulatory authorities where it is relevant to my taking part in research; I give permission for these individuals to have access to my records. ☐
4. I understand that my medical data will be collected for this study and may be used to help develop new research, and that data protection regulations will be observed and strict confidentiality maintained. ☐
5. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Researcher taking consent	Date	Signature

1 copy for patient; 1 for NYCTRU; 1 to be kept with hospital notes

Appendix 3

Patient information sheet

(Form to be on hospital headed paper)
Version 2, January 2003

ARIA Trial
Investigating the maternal anxiety experienced when waiting for amniocentesis results

Introduction
You are being invited to take part in a research study. Before you decide whether or not to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
We want to investigate different ways of reducing anxiety while waiting for the results of amniocentesis tests.

Why have I been chosen?
Because you are planning to, or have just undergone, an amniocentesis test. About five hundred people, like yourself, will be invited to take part.

Do I have to take part?
It is up to you. If you decide to take part you will be given this information sheet to keep and asked to sign a consent form. You will still be free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

What will happen to me if I take part?
The aim of this study is to assess the influence of two different ways of giving amniocentesis results on any anxiety you may have.

One way is to do the laboratory test in two parts. The first part involves the use of an early procedure, either Fluorescence In-Situ Hybridisation (FISH) or Polymerase Chain Reaction (PCR), which gives a partial result, including information about the more common chromosomal abnormalities such as Down's Syndrome, after 1–4 days. The second part of the test (the standard culture procedure) will still need to be performed to give the full results. Both the standard test and the early, partial test can be done on the single sample collected at amniocentesis.

The second way concerns the timing of giving out the final full analysis results. At the moment hospitals vary in how they do this. Some units give the result out as soon as the lab has processed it. This could be as quick as seven to ten days but could be 18–21 days. Other hospitals believe that the unpredictable nature of this is unfair and so release the results on a fixed day, often on Day 18. No one knows which method reduces your overall anxiety.

If you agreed to take part in this study, the combination you will be allocated to will be decided independently by a computer, which has no information about the participants (that is, by chance).

You will receive one of the four possible combinations:

- Full results will be given 18 days following your amniocentesis; no early, partial test will be carried out.
- Full results will be given 18 days following your amniocentesis; you will also have an early partial test so you will receive some results 1–3 days following your amniocentesis.
- Full results will be given as soon as they are available; no early, partial test will be carried out.
- Full results will be given as soon as they are available; you will also have an early, partial test so you will receive some results 1–3 days following your amniocentesis.

Whatever group you are allocated to, you will be asked to complete baseline questionnaires and a daily diary, which includes a short questionnaire about anxiety. You will also be sent a questionnaire one month after you received your test result. The research midwife may contact you by telephone after you receive your result, to see if you have had any problems completing your questionnaire and

to remind you to return it. Some women (25–50) will be asked to take part in a telephone interview at the same time. The interview will last about half an hour. It will be tape-recorded to allow the interviewer to play back the interview and take accurate notes. The recording will only be available to the research staff and will be destroyed at the end of the study. Your responses would not be fed back or reported in any way that could identify you as an individual.

What do I have to do?
Complete the initial questionnaires, diary and follow-up questionnaire one month after you have received your results. There is no drug or procedure being tested. However, recording your feelings may affect how you feel.

What if something goes wrong?
If taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then the usual NHS compensation arrangements apply. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you.

Will my taking part in this study be kept confidential?
Your GP will be notified of your participation in this research. All information collected about you during the course of the research will be kept strictly confidential.

What will happen to the results of the research study?
The time when women are waiting for amniocentesis results can be difficult for many women. We hope to gain a better understanding of how we can improve this and assess the impact of new technologies. The results will be published in a scientific journal. You will not be identified in any report or publication.

Who is organising and funding the research?
The National Health Service: Health Technology Assessment Programme.

Contact for further information about the trial (or if you no longer wish to be involved in the study)
Clare Jones (Trial Research Midwife), University of Leeds, 15 Hyde Terrace, LS2 9LT
Telephone: 0113 343 2722

If you have any queries relating to your condition or medical treatment, please contact:

……

……

……

……

……

……

You will be given a copy of this information sheet and a signed consent form to keep.

Appendix 4

Telephone transcripts

Rapid test results

Successful analysis

Hello, is that/can I speak to [woman's name]?

My name is Clare Jones and I am the research midwife for the ARIA study, ringing from Leeds. I have been asked to phone the results of the early analysis of your amniocentesis test.

As you know, this was only a partial result and has only tested for the most common chromosomal abnormalities; however, your result so far is normal.

The test has excluded almost all cases of babies with Down syndrome and also the next most common chromosome abnormalities, such as Edwards and Patau syndrome, but could miss one of the rarer abnormalities. We need to wait for the full amniocentesis result to be absolutely sure.

Can I just check that you have no questions about the diary?…

Thank you, I will phone you again with your full result at the appropriate time.

Failed analysis

Hello, is that/can I speak to [woman's name]?

My name is Clare Jones and I am the research midwife in the ARIA study, ringing from Leeds. I have been asked to phone you about the early analysis of your amniocentesis test.

This should have been able to give you a partial result today. Unfortunately, due to technical difficulties, the lab. was unable to obtain a result. However, they are still continuing with the conventional culture method and so you should still receive the full result in due course.

Can I just check that you have no questions about the diary?…

Thank you, I will phone you again with your full result at the appropriate time.

Welcome telephone call for women not randomised to receive a rapid test

Hello, is that/can I speak to [woman's name]?

My name is Clare Jones and I am the research midwife in the ARIA study, ringing from Leeds. I am just phoning to introduce myself and to thank you for taking part in the trial.

Can I just check that you have no questions about the diary?…

Thank you, I will phone you again with your result at the appropriate time.

Appendix 5

Trial steering committee

Janesh Gupta (Chair)
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Appendix 6

Trial management group

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Appendix 7

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Appendix 8

Missing data

This appendix contains all the details on the level of missing data for each of the end-points and the reasons and methods of imputation of missing data for each end-point. It is unknown whether women miss days in their diaries when they are particularly anxious or whether they simply forget. If women miss days in their diaries when they are more or less anxious some bias may be introduced.

Primary end-point

Women with more than two consecutive days' data missing within the waiting period were excluded from the primary end-point analysis. *Table 53* summarises the missing data for the primary end-point. In some cases whole diaries were missing and in other cases diaries had more than two consecutive days' data missing and therefore were not evaluable for the primary end-point. In total 194/218 (89%) diaries were returned, and of the 24 diaries that were missing a larger proportion of these were from the no Rapid test group (15%) than the Rapid test group (6%). This differential return rate had been identified during the monitoring of the trial and to address this imbalance a 'welcome to the trial' telephone call was introduced on 1 January 2004 for the no Rapid test group. *Table 53* shows the rate of missing diaries prior to 1 January 2004 compared with afterwards.

It can also be seen that there are fewer evaluable data for the no Rapid test group. This could be a source of potential bias: if women that are particularly anxious (or not) have missing data, this could potentially influence the findings of the trial; however, it may simply be that women were forgetting to complete their diaries.

Table 54 shows the level of missing data for the primary end-point.

Table 55 summarises the frequency of missing diary data by day. In total 59/194 (30.4%) diaries have some missing data, including 39 no Rapid test women versus 20 for Rapid test women. The rate of missing diary data between the fixed- versus variable-date women is 30 versus 29. Of the 59 diaries that have some missing data, 13 cannot be used for the primary end-point analysis as they have more than two consecutive days' data missing; again, there is a differential in the rate between Rapid and no Rapid test women (3 versus 10), and the rate is again very similar for fixed-

TABLE 53 *Rate of missing diaries before and after the 'welcome to the trial' telephone call*

	Missing diaries		
	Before the phone call	**After the phone call**	**Overall**
Rapid test	3/63 (5%)	4/44 (9%)	7/107 (7%)
No Rapid test	11/70 (16%)	6/41 (15%)	17/111 (15%)
Fixed date	4/68 (6%)	6/44 (14%)	10/112 (9%)
Variable date	10/65 (15%)	4/41 (10%)	14/106 (13%)

TABLE 54 *Missing data for the primary end-point by intervention factor*

	Rapid test ***n*** **= 107**	**No Rapid test** ***n*** **= 111**	**Fixed date** ***n*** **= 112**	**Variable date** ***n*** **= 106**	**Total** ***n*** **= 218**
Diaries received	100 (94%)	94 (85%)	102 (91%)	92 (87%)	194 (89%)
Diaries missing	7 (6%)	17 (15%)	10 (9%)	14 (13%)	24 (11%)
Diaries not evaluable for primary end-point	3 (3%)	10 (9%)	6 (5%)	7 (7%)	13 (6%)
Diaries used in primary end-point analysis (% of those expected)	97 (91%)	84 (76%)	96 (86%)	85 (80%)	181 (83%)

TABLE 55 *Missing data by day*

Day	Rapid test	No Rapid test	Fixed date	Variable date	Total
1	7	16	12	11	23
2	0	6	3	3	6
3	0	7	3	4	7
4	1	6	2	5	7
5	2	5	3	4	7
6	2	6	4	4	8
7	3	6	4	5	9
8	3	7	4	6	10
9	3	6	3	6	9
10	4	6	4	6	10
11	5	7	4	8	12
12	5	5	3	7	10
13	4	6	3	7	10
14	4	6	4	6	10
15	3	5	2	6	8
16	4	5	2	7	9
17	5	11	4	12	16
18	4	8	3	9	12
19	8	10	6	12	18
20	8	9	5	12	17
21	11	13	9	15	24
Total days missing	86	156	87	155	242
No. of diaries with missing data	10	15	20	14	59

TABLE 56 *Frequency of important diary days missing by intervention factor*

	Rapid test	No Rapid test	Fixed date	Variable date	Total
Day 1 only missing	6	9	8	7	15
Results day only missing	1	6	3	4	7
Days 19/20/21 only missing	4	5	6	3	9
After day 3 or 4 missing	2	1	1	2	3
Whole diary missing	0	3	1	2	3

TABLE 57 *Percentage of missing day 1 data by intervention factor*

	Rapid test	No Rapid test	Fixed date	Variable date	Total
Missing day 1 data	7/97 (7%)	11/84 (13%)	9/96 (9%)	9/85 (11%)	18/181 (10%)

versus variable-date women. Three of the 13 diaries that are unusable for the primary end-point are completely blank and are all from the no Rapid test women.

Of the 59 diaries with missing data, 23 (39%) have day 1 data missing; this is the amniocentesis test day. There are 16 no Rapid test women with missing day 1 compared with 7 Rapid test women. The rate of missing day 1 data is very similar for fixed- and variable-date women. Day 21 is also frequently missed, 24/59 (41%), that is, after the karyotype result has been issued. The differential rate for missing day 21 is similar for Rapid and no Rapid test women (11 versus 13); however, there is a difference between fixed- and variable-date women (9 versus 15). *Table 55* shows missing data by day.

Tables 56 and *57* summarise the frequency of diaries that have important diary days' data missing. Day 1 is the amniocentesis test day itself; all women have undergone the same invasive test which carries the same risk to their pregnancy, they have all also agreed to be randomised to a randomised controlled trial. Their main anxiety is

expected to be around the procedure and therefore it has been assumed that their anxiety levels will be similar across the interventions. Although they will be aware of their randomisation result and some women may be disappointed in their randomised allocation, it seems reasonable to assume that anxiety levels on day 1 will be consistent within the intervention group. Karyotype result day is another important day for women. The frequency that karyotype result day is missed in the diaries is also shown. It was expected that women may stop completing their diaries once they have their karyotype result. *Table 56* shows the frequency of women not completing days 19/20/21; after day 18 all fixed-date women should have their results and also the majority of variable-date women. It can be seen that more fixed-date women stop completing their diaries after day 18 than variable-date women. It was also expected that women receiving a rapid test may stop completing their diaries once they had received this result.

Although there appears to be a difference in the differential diary return rates and level of missing data between Rapid and no Rapid test women, there is no evidence to indicate that these women are more or less anxious.

Imputation of missing data

Missing data for up to two consecutive days has been imputed using interpolation. For women with missing data on results day only, the previous day's anxiety score has been carried forward. This is a conservative imputation as women are expected to be more anxious the day before results day than on results day. For patients with missing data on day 1 (amniocentesis day) but with day 2 data available, the intervention group average for day 1 has been imputed. The intervention groups are Rapid test, fixed date; Rapid test, variable date; no Rapid test, fixed date; and no Rapid test, variable date. The impact of this was investigated using the following sensitivity analyses;

- Exclude those with day 1 missing.
- Define the waiting period from day 2 to results day for everyone.
- Impute best scores (low anxiety score) for no Rapid test patients and worst scores (high anxiety score) for Rapid test patients.

Of the 181 evaluable diaries, 18 patients had missing data on day 1 only. *Table 57* details the percentage of missing day 1 data by intervention factor. The rate of missing day 1 data is slightly higher for no Rapid test patients; this reflects the overall pattern of the differential return rate of diaries and the general pattern of missing diary data.

Table 58 details the baseline characteristics for women who do not complete day 1 compared with those who do. As the numbers are small, some differences are expected; in terms of age, gestation, first pregnancy and many of the other baseline characteristics the two populations are comparable. However, there may be a difference in the two populations in two areas; women missing day 1 are less likely to have had a previous amniocentesis, 6% compared with 13% of patients that complete day 1, and 11.1% have had a previous miscarriage compared with 3%.

Secondary end-points

Peak anxiety during the waiting period

All returned diaries that contain some data are to be used for this end-point. This end-point is the peak in women's anxiety during the waiting period, hence no imputation of missing data has been carried out for this secondary end-point. This analysis does not consider how many times that peak score is reached.

Length of time to the peak anxiety

Again, all returned diaries that contain some data are to be used for this end-point. This end-point is the length of time to the first peak in women's anxiety during the waiting period, hence no imputation of missing data has been carried out. This analysis does not consider how many times that maximum score is reached.

Total anxiety in 11 days following amniocentesis

Table 59 shows the level of missing diary data in the 11 days following the amniocentesis. This end-point compares the total anxiety for these 11 days; women with more than two diary days data missing have been excluded from the analysis for this end-point. Five of the six women with 3 or 4 days' data missing have two or more consecutive days data missing and were also excluded from the primary end-point analysis. For the women with 1 or 2 days' data missing, the average score for the days completed has been imputed for the missing days.

Average anxiety from day 12 to karyotype results day

This end-point has been analysed using the SAUC, hence for women with 1 or 2 days' data

TABLE 58 *Baseline characteristics for women with missing day 1 data compared with those completing day 1*

	Missing day 1 data ***n* = 18**	**Complete day 1 data** ***n* = 163**
Age (years): <35	5 (28%)	54 (33%)
≥ 35	13 (72%)	109 (67%)
Ethnic origin:		
White	18 (100%)	151 (93%)
Black Caribbean	0 (0%)	1 (1%)
Black African	0 (0%)	1 (1%)
Indian	0 (0%)	6 (4%)
Asian other	0 (0%)	1 (1%)
Other	0 (0%)	3 (2%)
First pregnancy:		
Yes	4 (22%)	41 (25%)
No	14 (78%)	122 (75%)
Women with previous pregnancies:	*n* =14	*n* =122
Previous miscarriage:		
Never	8 (57.1%)	78 (63.9%)
Once	4 (28.6%)	39 (32.0%)
More than once	2 (14.3%)	5 (4.1%)
Previous stillbirth:		
Never	14 (100.0%)	118 (96.7%)
Once	0 (0.0%)	4 (3.3%)
More than once	0 (0.0%)	0 (0.0%)
Previous serious abnormality:		
Yes	1 (7.1%)	8 (6.6%)
No	13 (92.9%)	114 (93.4%)
Prenatal Screening:		
Yes	7 (50.0%)	64 (52.5%)
No	7 (50.0%)	58 (47.5%)
Previous amniocentesis:		
Yes	1 (7.1%)	21 (17.2%)
No	13 (92.9%)	101 (82.8%)
Do you have children?		
Yes	9 (64.3%)	114 (93.4%)
No	5 (35.7%)	8 (6.6%)
Gestation (weeks): mean (SD)	16.3 (1.2)	16.2 (1.1)
Previous pregnancies: mean (SD)	2.6 (1.4)	2.6 (1.5)
How many children?		
Median (IQR)	2 (1, 2)	2 (1, 2)
Missing	5 (35.7%)	8 (6.6%)
Age (years)		
Mean (SD)	36.2 (5.6)	36.1 (3.9)
Missing	0 (0.0%)	0 (0.0%)

IQR, interquartile range.

missing data have been imputed using interpolation. *Table 60* shows the level of missing data. Six women with more than two consecutive days' data missing between day 12 and karyotype results day have been excluded from this end-point: three women had received their results prior to day 12 and therefore do not have any data after day 12.

Total anxiety from amniocentesis day to day 21

Table 61 shows the level of missing diary data for

TABLE 59 *Missing data for 11 days following amniocentesis*

	Included	Excluded	Total
One day only missing	29	0	29
Two days missing	1	0	1
Three days missing	0	2	2
Four days missing	0	4	4
Seven days missing	0	2	2
Eight days missing	0	1	1
All 11 days missing	0	3	3
Missing diaries	0	24	24
Complete for 11 days	152	0	152
Total	182	36	218

TABLE 60 *Missing data from day 12 to karyotype result*

	Included	Excluded	Total
>2 consecutive days missing	0	6	6
≤2 consecutive days missing	185	0	185
Results issued prior to day 12	0	3	3
Missing diaries	0	24	24
Total	185	33	218

this end-point. Women with more than 3 days' data missing were excluded from the analysis, and the average daily score was imputed for women with ≤3 days' data missing.

Total anxiety for the first 4 days

Table 62 shows the level of missing data for this end-point. Twenty-three patients have day 1 data missing; of these, 18 only have day 1 missing. Patients that have more than one day's data missing have been excluded from the analysis of this end-point.

Total anxiety for the 7 days prior to karyotype results day

Table 63 shows the level of missing data in the last 7 days prior to the karyotype result. Women with more than 2 days' data missing will be excluded from the analysis of this end-point. For women with 1 or 2 days data missing, the average score for the completed day's data has been imputed.

Recalled anxiety

Missing data were treated as missing at random for this end-point. However, only one woman had not completed the day 10–12 question. All 175 women that had returned questionnaires in the correct time frame had completed the 2–3 days before the karyotype result question.

TABLE 61 *Missing data up to day 21*

No. of days missing	Included	Excluded	Total
1	29	0	29
2	3	0	3
3	5	0	5
4	0	6	6
5	0	4	4
6	0	4	4
7	0	1	1
9	0	1	1
16	0	1	1
17	0	1	1
18	0	1	1
All 21	0	3	3
Missing diaries	0	24	24
Complete for 21 days	135	0	135
Total	172	46	218

TABLE 62 *Missing data for 4 days following amniocentesis*

	Included	Excluded	Total
One day only missing	19	0	19
Two days missing	0	1	1
Three days missing	0	2	2
All four days missing	0	4	4
Missing diaries	0	24	24
Complete for 4 days	168	0	168
Total	187	31	218

TABLE 63 *Missing data for 7 days prior to karyotype result*

	Included	Excluded	Total
One day only missing	10	0	10
Two days missing	3	0	3
Three days missing	0	2	2
Six days missing	0	1	1
All seven days missing	0	6	6
Missing diaries	0	24	24
Complete for 7 days	172	0	172
Total	185	33	218

Anxiety at 1-month follow-up

Missing data were treated as missing at random for this end-point; however, one woman (no Rapid test, fixed date) had not completed this question at all, another (no Rapid test, variable date) had only circled responses for three out of the six questions.

Appendix 9

Sensitivity analyses

Introduction

This appendix contains all the details and results of the four sensitivity analyses that were carried out around the primary end-point.

Scenarios

Scenario A – Excluding all 18 women who do not have day 1 data

This analysis excluded all the 18 women who did not complete day 1 data.

Scenario B – Defining the waiting period from day 2 to results day

This analysis defined the waiting period for all women as from day 2 to standard culture results day for all women.

Scenario C – Imputing best and worst

This analysis imputed the best possible anxiety score, that is, low score (6), for no Rapid test women and the worst possible anxiety score, that is, high score (24), for Rapid test women, for day 1.

Sensitivity analysis – variable-date women

An additional sensitivity analysis was undertaken, this time excluding the 22 variable-date women who did not receive their standard culture result on the date it became available.

Average anxiety during the waiting period

Table 64 summarises the SAUC during the waiting period of the daily anxiety scores on a 19-point scale with scores ranging from 6 to 24, for each of the four scenarios. A higher score shows higher anxiety.

Unadjusted analysis

An unadjusted analysis was undertaken for each of the four scenarios using a linear regression procedure in SAS; the factorial design of the trial was taken into account and each of the factors within the factorial design was adjusted for, that is, Rapid test versus no Rapid test, and fixed date versus variable date. The results are shown in *Table 65*.

Table 65 confirms the results of the primary analysis. Although the adjusted means and standardised effect sizes vary slightly, the results are in the same direction and have the same level of statistical significance, confirming the robustness of the data and of the findings reported for the primary end-point analysis.

TABLE 64 *Anxiety scores for women on each of the four interventions*

Intervention	Rapid test	No Rapid test	Fixed date	Variable date
Scenario A – Excluding all 18 women who do not have day 1 data				
n	100	100	103	97
Mean (SD)	11.0 (2.4)	13.3 (3.6)	11.9 (3.2)	12.2 (3.2)
Median (min., max.)	11.1 (5.8, 17.1)	13.1 (6.1, 21.7)	11.8 (6.1, 18.9)	12.0 (5.8, 21.7)
Missing	10	27	16	21
Scenario B – Define the waiting period from day 2 to results day				
n	107	111	112	106
Mean (SD)	10.2 (2.3)	12.4 (3.3)	11.1 (3.0)	11.4 (3.0)
Median (min., max.)	10.4 (5.3, 15.8)	12.4 (5.8, 20.5)	10.9 (5.8, 17.9)	11.2 (5.3, 20.5)
Missing	10	27	16	21

continued

TABLE 64 *Anxiety scores for women on each of the four interventions (cont'd)*

Intervention	Rapid test	No Rapid test	Fixed date	Variable date
Scenario C – Imputing best and worst				
n	107	111	112	106
Mean (SD)	11.1 (2.4)	13.2 (3.4)	11.9 (3.1)	12.3 (3.1)
Median (min., max.)	11.2 (5.8, 17.1)	13.1 (6.1, 21.7)	11.8 (6.1, 18.9)	12.1 (5.8, 21.7)
Missing	10	27	16	21
Sensitivity analysis – variable women				
n	91	105	112	84
Mean (SD)	10.9 (2.4)	13.3 (3.3)	11.9 (3.1)	12.4 (3.1)
Median (min., max.)	11.1 (5.8, 17.1)	13.2 (6.1, 20.9)	11.8 (6.1, 18.9)	12.1 (5.8, 20.9)
Missing	7	26	16	17

TABLE 65 *Results of the analysis, only adjusting for the factorial design for each scenario*

Comparison	Included in analysis	Missing	Adjusted mean (SE)	Scale score difference (95% CI)	*p*-Value	Standardised effect size (95% CI)
Scenario A – Excluding all 18 women who do not have day 1 data						
Rapid test vs no Rapid test	163	37	11.04 (0.32) 13.31 (0.35)	2.27 (1.34 to 3.21)	<0.0001	0.76 (0.45 to 1.07)
Fixed date vs variable date	163	37	12.08 (0.32) 12.33 (0.35)	–0.32 (–1.25 to 0.62)	0.5048	–0.11 (–0.42 to 0.21)
Scenario B – Define the waiting period from day 2 to results day						
Rapid test vs no Rapid test	181	37	10.19 (0.28) 12.44 (0.30)	2.25 (1.43 to 3.07)	<0.0001	0.81 (0.51 to 1.10)
Fixed date vs variable date	181	37	11.19 (0.29) 11.44 (0.30)	–0.24 (–1.06 to 0.58)	0.5614	–0.09 (–0.38 to 0.21)
Scenario C – Imputing best and worst						
Rapid test vs no Rapid test	181	37	11.07 (0.29) 13.25 (0.32)	2.18 (1.32 to 3.04)	<0.0001	0.75 (0.45 to 1.04)
Fixed date vs variable date	181	37	11.98 (0.30) 12.34 (0.32)	–0.36 (–1.22 to 0.50)	0.4070	–0.12 (–0.42 to 0.17)
Sensitivity analysis – variable women						
Rapid test vs no Rapid test	163	33	10.97 (0.32) 13.29 (0.33)	2.33 (1.43 to 3.22)	<0.0001	0.81 (0.49 to 1.12)
Fixed date vs variable date	163	33	11.99 (0.30) 12.27 (0.35)	–0.28 (–1.19 to 0.63)	0.5473	–0.10 (–0.41 to 0.22)

SE, standard error.

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We look forward to hearing from you.

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