UK National Screening Committee

First trimester combined screening for T13 and T18

Purpose

1. This paper provides background on the agenda item addressing first trimester screening for trisomy13 (T13) and trisomy 18 (T18) using the combined test.

Current policy

2. The current policy is that screening for T13 and T18 is recommended as part of the 2nd trimester fetal anomaly scan.

Current review

3. The implementation of the combined test for T21 has stimulated interest in adding first trimester screening algorithms for T13 and T18.

4. This is the first time the UK National Screening Committee (UK NSC) has formally considered first trimester screening for these two conditions.

5. However previous advice, captured in the Model of Best Practice (2011), was that the evidence for screening in the first trimester was 'insufficiently robust'. This statement emphasised maternal serum screening and was based on a review of the evidence undertaken by the Socio-economic Research and Intelligence Observatory (SERIO).

6. Since then the NHS Fetal Anomaly Screening Programme (FASP) has proposed that first trimester screening using the combined test should be considered for implementation in the UK and has consulted on a proposal to take this forward.

7. The current review focuses on studies of the combined test which were published since the SERIO review, January 2009 – November 2012. Earlier versions of the review were considered by the FASP Steering Group and the Fetal, Maternal and

Child Health Screening Subgroup (FMCH). Subsequent discussion was based on the comments received from both groups.

Review conclusions

8. The review highlights that T13 and T18 are currently detected at several points in the antenatal care pathway. This includes detection of the conditions as a finding from the diagnostic follow up of women found to be at high risk of T21 through the completed combined test and as a result of invasive testing in women referred on the basis of the nuchal translucency measurement alone.

9. Some key points identified by the review are that:

- logistically the addition of combined test T13 and T18 algorithms is feasible and has been shown to produce a higher detection rate in comparison to use of T21 algorithms alone
- this does not appear to significantly increase the false positive rate
- there is uncertainty on the type of algorithm and the optimum cut offs which might be used
- studies focus on the completed combined test but practice in the UK also includes the use of Nuchal Translucency =/> 3.5mm as an independent marker of risk
- no studies explored the way this might impact on completion of the combined test, the additional value of including T13 and T18 algorithms in combined test packages or on current assumptions regarding the characteristics of the completed combined test.

10. As such, while first trimester screening for T13 and T18 using the combined test appears to be a feasible option, the identification of the precise strategy for its practical application appears complicated by a number of issues. Most importantly these relate to the way in which risk arising from nuchal translucency measurement might be handled. This is further complicated by ongoing work in the area of Non Invasive Prenatal Testing (NIPT) which is likely to report at the end of this year.

Consultation

11. A three month consultation was hosted on the UKNSC website. Thirty four stakeholder organisations were contacted directly. These are listed on the UK NSC website. Responses were received from the Royal College of Obstetricians and Gynaecologists / British Maternal and Fetal Medicine Society, British Isles Network of Congenital Anomaly Registers, The Association for Clinical Genetic Science, Wolfson Institute of Preventive Medicine, PHG Foundation, SOFT UK, Society and

College of Radiographers, Royal Devon & Exeter Hospital, three individual health professionals. These are attached for information.

12. No respondents objected to the aim of screening for T18 and T13 in the first trimester and the increased detection rate from the combined test compared to current practice appears to be accepted. Responses included the following points:

- the addition of T18 and T13 algorithms to current screening packages would be unlikely to significantly increase the false positive rate, the number of unnecessary invasive tests or the workload of sonographers. However a publication submitted by one respondent estimated that a separate T13 algorithm would add very little to the detection rate achieved by a T21 and T18 algorithm
- a formal combined test screening strategy would help standardise the current, ad hoc, arrangements for first trimester detection of T18 and T13. However the current mechanisms for detection were viewed as a potentially viable option by one respondent and the detection rate within it was highlighted by others
- earlier screening with high quality counselling would help improve the experience women and families affected by these conditions. However the complexity of reporting risk for the three conditions was noted by several respondents and different options were suggested for consideration
- that current diagnostic testing with QF PCR was set up to detect sex chromosome aneuploidies (such as Turner Syndrome) and cases of triploidy. The detection of these conditions in some screen positive women would be difficult to change. Another response suggested that detection of T18 and T13 during the 18 – 20 week scan should be reconsidered as screening in the first trimester was likely to reduce the prevalence of the conditions in the second trimester.

Recommendation

13. At its meeting on June the 18th the UK NSC agreed that first trimester screening for T18 and T13 using the combined test should be recommended unless significant concerns were raised through the consultation. No such concerns have been raised.
14. It is recommended that:

- First trimester screening using the combined test should be recommended by the UKNSC.
- FASP should be asked to consider the issues raised by the review and the consultation, for example to the algorithm, risk reporting strategy, management of raised NT, issues relating to the diagnostic test and the 18 – 20 + 6 week scan
- A report should be presented to the next meeting of the UKNSC addressing key issues in the implementation strategy.

UK National Screening Committee

First trimester combined screening for trisomy 18 and trisomy 13

Consultation comments

June 2014

1.

Organisation:			
Name:	Julie Poultney	**Email address:**	[redacted]
Please tick whether you are making this submission as an individual or on behalf of an organisation. **Individual**√ **Organisation** ☐			

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
N/A	Clarification re T13 and T18 in second trimester serum screening or just first trimester combined.	Think the consultation is good and we should screen for these conditions in both combined screening in first trimester and serum screening in second trimester

2.

Organisation:	University Hospital of Leicester		
Name:	Louise Payne	**Email address:**	[redacted]
Please tick whether you are making this submission as an individual or on behalf of an organisation. **Individual x** **Organisation** ☐			
Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*	
	Overall proposal to move to 1st trimester screening	Supportive of this as it takes place informally and almost on an 'ad hoc' basis now when women are often unaware of this. Open and honest policy with good patient information would be an improvement	

3.

Organisation:	Nottingham University Hospitals NHS Trust		
Name:	Dr Pam Loughna	**Email address:**	[redacted]
Please tick whether you are making this submission as an individual or on behalf of an organisation. **Individual X** **Organisation** ☐			
Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*	
		Excellent proposal. I have no adverse comments, only support.	

4.

Organisation:	Royal Devon & Exeter Hospital		
Name:	Adrian Cudmore	**Email address:**	[redacted]
Please tick whether you are making this submission as an individual or on behalf of an organisation. **Individual** ☐ **Organisation** ☒			

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
Section 1 page 5	**1. The condition should be an important health problem**	The fact that this is a given and there is a proven methodology to detect most affected pregnancies in the first trimester, when intervention is far less invasive makes the case for its introduction within the routine combined screen.
Section 2 page 5	*The report also shows that 52% of trisomy 13 and 55% of trisomy 18 cases were detected by first trimester screening, 15% and 16% respectively by second trimester screening, and 25% and 20% during ultrasound scans.*	It is quite feasible that 20-25% of affected pregnancies could have been detected in the first trimester, merely by applying the relevant risk calculations to data already generated by the combined screen. This represents not only a waste of resource, but a lack of good patient care – I doubt many mothers to be know this, nor would they support it. This is further exemplified by the fact that so many cases are already being detected by combined screening outside of the NSC standards.
Table 1 Page 8	**Table 1: Cases of trisomy 13 and 18 in England and Wales 2010 and 2011 by outcome**	The very low number of live births and high proportion of terminations following pre-natal diagnosis, illustrates clearly the preference of our users. Is there evidence that they have a preference for ealier intervention? If so, and anecdotally I

		suspect that is the case, that is further strong evidence for its inclusion in combined screening. Currently that choice is not available to half of mothers.
Section 5 Page 13	**5. There should be a simple, safe, precise and validated screening test**	The test is already available and being performed for all pregnancies. Widely accepted that screening efficiency for T18 and T13 is better than for T21.
Section 7 Page 40	**Criterion 7: Unclear if met**	50% of pregnancies are already being screened in the first trimester for the fatal trisomies T18 & T13 and all should be being offered screening for T21. It is difficult to understand how there would any increased unacceptability for offering full screening to all.
Section 8 Page 41	**Criterion 8: Partially met.**	This is easily remedied and should not be a block to screening.

5.

Organisation:	Society and College of Radiographers		
Name:	Nigel Thomson, Professional Officer, Ultrasound.	[redacted]	

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Individual ☐ **Organisation** ☐

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
General		Although sonographers are aware of the structural abnormalities associated with T13/T18 at the first trimester screening scan it would be good to have specific materials prepared to support any extension of screening to include these two conditions. These could be on-line resources similar to those currently available for T21 screening. In particular descriptions and images of exomphalos, holoprosencephaly and megacystis could be included along with details of the T13/T18 chromosomal abnormalities themselves.
General		The proposed test should not require an increase in sonographer time or additional ultrasound resources; these are already at a premium. If it were to do so additional funding for training and staff must be available before commencing.
15		It would be regrettable if there was an increase in the numbers of invasive procedures required (amniocentesis and CVS). Recent years have seen a welcome reduction in the number of invasive tests associated with T21 screening which can lead to the miscarriage of a normal fetus. This is discussed on Page 15.

6.

Organisation:	SOFT UK		
Name:	Kirsty Bassett	**Email address:**	[redacted]

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Individual ☐ **Organisation** ☒

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
Section 8, pp40-41	There should be an agreed policy on the further diagnostic investigation of individuals with a positive result and on the choices available to those individuals.	We had a number of responses from SOFT families (families affected by T13, T18, and related conditions) who were concerned with the lack of consistency in the tests available to pregnant women. More than half of respondents had not been offered NHS screening for the affected pregnancy. In one case this was because she was carrying twins and, for health reasons, had frequent early scans that suggested a problem. Two other respondents were not offered screening because of previous healthy pregnancies. A number of respondents paid for private tests as they were not available to them on the NHS. In one case, an amniocentesis was preformed following a private nuchal fold scan. In another they had private blood screening following a higher risk result of Downs from an NHS nuchal fold scan. Because of the lack of screening all respondents felt the impact of a later diagnosis. One mother did not find out until after the birth of her baby as her one routine scan did not indicate a

		problem. Another noted that her decision would have been the same but she felt that the impact of her choice would have been less if she had received a diagnosis at 13 weeks rather than 17 weeks.
Section 8	Importance of offering counselling before a termination	SOFT families are quite often offered a termination without counselling. They feel that it is important that families are allowed the time they require to make any decision regarding carrying on with a pregnancy or opting for a termination. Many feel expected to make decisions very quickly without adequate time being given for informed discussions. One SOFT family felt pressured into having a selective termination following a misdiagnosis of Downs syndrome after a nuchal fold scan. Other families have reported a feeling of being put straight on to a termination “conveyor belt” as soon as the diagnosis is received. Even families who, in hindsight, are content with their decision to choose a termination still felt that they were expected to have one and were treated accordingly.

7.

Organisation:	PHG Foundation		
Name:	Alison Hall	**Email address:**	[redacted]

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Individual ☐ **Organisation x**

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Conclusion; The condition; p.47	'Among the cases detected prenatally, the indication for diagnosis in over half (54% with trisomy 13 and 70% with trisomy 18) was reported to be first trimester screening'.	Existing first trimester screening programmes for DS may prompt diagnostic tests which result in prenatal detection of T13 (54%) and T18 (70%) as a by-product of those screening programmes. This could be described as opportunistic screening for these conditions within the T21 programme.
Conclusion; The condition; p47	'A separate analysis of national data from 2008 suggested that about 27% of cases of T13 and T18 had been identified as a result of raised NT alone'	This statement suggests that an additional cohort of T13 and T18 cases are being detected through first trimester NT screening. Although they have not been described as such in the review, these findings are unsolicited, yet clinically actionable, since they are outside the formal scope of the T21 screening programme. Consistent with the ethical and legal debate about the generation and communication of unsolicited findings or incidental findings in other fields, informed choice and consent processes and documentation should reflect the fact that a finding of T13 or T18 is a possible outcome of the combined screening programme for fetal anomaly in the first trimester. This degree of transparency is not only good practice, but safeguards the autonomous choices of women who are offered

		screening.

8.

Response from Professor N Wald, Wolfson Institute of Preventive Medicine

Response to UK NSC consultation document 'First trimester combined screening for trisomy 13 and trisomy 18'

The document considers, in detail, the prevalence of pregnancies with Trisomy 13 (T13) and Trisomy 18 (T18) and the extent to which these disorders can be identified using the first trimester screening markers (NT, free ß-hCG and PAPP-A). No clear conclusion is drawn on whether the antenatal detection of T13 and T18 is justified.

1. The conclusion states that there have been no major changes to the evidence since the 2010 SERIO review. However further evidence has been published, for example, Bestwick et al (2012) – copy attached[1]. This paper covers several of the points raised in the conclusion 'Implications for research'. It would be appropriate for the document to be updated with the new evidence.

2. To be comprehensive the document should include algorithms that use quadruple and integrated test markers as well as combined test markers.

3. There is no reason why T13 and T18 should not be detected as an incidental effect of screening for T21 as is done in practice. The key question is 'Should separate algorithms be used to improve the detection of T13 and T18 provided this does not lead to a clinically significant increase in the amniocentesis/CVS rate?' The conclusion of Bestwick et al is that this is the case for T18 and probably also the case for T13 (see table 1 in the attached paper).

4. An important practical question is the reporting of risks. If, in effect, 3 disorders are being screened for (T21, T18 and T13) reporting separate risks for each disorder could lead to an inappropriate increase in the false-positive rate with little or no improvements in detection rate. Consideration should, therefore, be given to a single risk estimate that relates to the pregnancy being affected with any one of these disorders. This approach would also avoid the incorrect assumption that individual risks can be added together to achieve a single risk estimate.

   Alternatively the screening policy could continue to be directed to the antenatal detection of Down's syndrome with the incidental reporting of risks for T13 and T18 limited to exceeding specified risk cut-offs (e.g. 1 in 100) which would lead to an increase in the amniocentesis/CVS rate of no more than about 0.2%.

[1] Copyright regulations prohibit the UKNSC from attaching the paper. The publication details are Jonathan P Bestwick, Wayne J Huttly and Nicholas J Wald; Detection of trisomy 18 and trisomy 13 using first and second trimester Down's syndrome screening markers, J Med Screen 2013;20:57–65

The problem of reporting risks for each disorder is screening units and patients maybe worried with risks of 1 in 200 and this could lead to an increase in the amniocentesis/CVS rate.

It may not be widely recognized that the same risk (e.g. 1 in 200) has different implications for different tests and different disorders in terms of detection rates and false-positive rates.

Therefore we conclude that the document could endorse:

- Incidental detection of T13 and T18 as part of a Down's syndrome screening programme.
- Separate algorithms for T18 and probably T13.
- Avoiding reporting separate risks for all results.
- Continued discussion over whether a single risk for any one of the abnormalities be used or report the risk for T21 with an alert for the risk of T18 or T13 that would not be identified through the T21 algorithm. The risk cut-off for such an alert should be determined so that there is an increase in the detection rate with a minimal increase in the false-positive rate.

We suggest that the document be appropriately revised and brought up to date.

Wolfson Institute of Preventive Medicine

30th June 2014

9.

Response from the RCOG / British Maternal and Fetal Medicine Executive Committee

8-9 responses were received from members of the BMFMS executive committee regarding the proposed first trimester screening for T13 and 18.

All were in broad agreement that it seemed a worthwhile and reasonable proposal. The evidence presented suggests, I think, that the added false positive rate will be only approx. 0.5% above and beyond that of the T21 screening programme. This is reassuring.

A regional audit had shown that >50% of cases were detected anyway because of an NT>3.5mm (East of England).

All agreed that T13 and 18 are very different conditions to T21, in view of the high attrition rates through pregnancy and the first year of life. Counselling couples about T13 and 18 is quite different to trisomy 21, and this might need to be reflected in how the risk data is presented to women choosing screening. Giving a woman the risk of her baby being liveborn with T13 or 18 underplays the very much greater risk of late intrauterine fetal death/stillbirth, complications such as polyhydramnios and the high chance of later diagnosis of severe anomalies, associated with T13 and T18, in contrast to trisomy 21.. Some respondents argued that the screening risk given to the woman should be the risk of the pregnancy being affected at the gestation when the test was performed (a key difference with the trisomy 21 risk), rather than the risk at delivery.

Kim Hinshaw took this idea further and suggested that we might present more than one risk to the woman; ie the risk at the time of testing and the risk at delivery, along with information on how many affected babies were still alive say at 1, 6 and 12 months of age.

Below is the table he suggested (with no values!). It could be simplified, and personalised to each woman and her risks based on her age , NT and biochemistry.

	Chances of a baby with the condition still being alive at different times during and after pregnancy								
	In early pregnancy (at about 8 weeks)	At time of testing (usually 11-13 weeks)	Halfway through pregnancy (at 20 weeks)	Three quarters of the way through pregnancy (at 30 weeks)	Near the end of pregnancy (at around 38-40 weeks)	1 week after birth	1 month after birth	6 months after birth	1 year after birth
Genetic problem									
T21 or 'Down Syndrome' (affects 1 in every xxx pregnancies at 12 weeks)	100%								
T18 or 'Edward's Syndrome' (affects 1 in every xxx pregnancies at 12 weeks)	100%								
T13 or 'Patau Syndrome' (affects 1 in every xxx pregnancies at 12 weeks)	100%								

We all feel that the key to this screening programme working well will be good quality information for the women and this will involve a significant education programme for midwifery and other maternity staff. T13 and T18 aren't simply 'like more severe cases of Down syndrome' as I have heard said before.

Hope that helps in some way

Alec

Alec McEwan
Consultant in Obstetrics and Fetal Medicine
Nottingham University Hospitals NHS Trust

On behalf of BMFMS Exec Committee

Organisation:	The Association for Clinical Genetic Science		
Name:	Sian Morgan	**Email address:**	[redacted]

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Individual ☐ **Organisation** √

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
P47 Conclusions	The test	A patient with an increased risk for T21 currently from Combined screening has at least a diagnostic QF-PCR test for T21, T18 and T13. In addition, triploidy and sex chromosome aneuploidy (e.g Turner) are reported following a QF-PCR result. A patient does not currently 'choose' her diagnostic result. The ACGS would like to point out that it be difficult for the genetic laboratories to support the 'either screen for T21 only, or T13/T18 only, or T21/T13/T18' first trimester combined screening pathways because: 1. we have been reporting QF-PCR diagnostic tests for T13,T18,T21,triploidy and sex chromosome aneuploidy routinely now for over 8 years as a single test. 2. all the tests accommodate this testing pathway i.e. the multiplex assays (primers) have been designed to accommodate this test. 3. it would be difficult to set up different assays logistically. This is a high throughput test in most laboratories with a very

		short turnaround time. 3. how would a QF-PCR result for a triploidy and sex chromosome aneuploidy fit in with an 'only T21' or 'only T18/T13' pathway? It does not make any reasonable sense. We would also like to add that it was disappointing to see no horizon scanning for other testing strategies within the document, namely NIPT.

Organisation:	British Isles Network of Congenital Anomaly Registers (BINOCAR)		
Name:	BINOCAR	**Email address:**	[redacted]

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Individual ☐ **Organisation** ☒

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
Page 47-53	Conclusions	BINOCAR Registers are strongly supportive of the introduction of first trimester screening for T13 and T18 as it provides: - Earlier screening, leading to increased options for reproductive choice. - Standardisation of the current ad hoc first trimester screening/diagnosis for T13 and T18. - Additional screening at a marginal cost following the existing investment in combined screening for T21 e.g. ultrasound training, resources, QA, etc. - Consistent screening programmes for aneuploidy as T13 and T18 share screening features with T21 including their amenability to detection by combined screening and NIPT, and the need for karyotyping to confirm diagnosis.
Pages 5-6	UK prevalence	The prevalence of T18 is increasing and will continue to increase if maternal age continues to rise. These conditions will increase in frequency, and therefore the need for a robust screening programme is important for an increasing number of families.

Page 12	Epidemiology and existing first trimester detection	Currently, a larger proportion of T18 and T13 are detected in the first trimester (70% and 54% respectively) than by the existing screening programme (fetal anomaly scan 13% T18 and 23% T13). [ref Consultation page 47] More recent evidence from a BINOCAR register[i] supports this finding.
Page 49	Implications for research	The role (if any) of 18-20 fetal anomaly ultrasound screening for T18 and T13 will need to be reviewed following a change to combined screening for T18 and T13. Detection rates/standards will change if the prevalence of T18 and T13 in the second trimester is reduced by combined screening or the management of NT >= 3.5mm.
Pages 54-57	Evidence/references	We welcome the use of BINOCAR data to inform the evaluation and changes to national antenatal screening programmes. Registers contributing evidence to this consultation include NDSCR and BINOCAR Hub.

[i] Tonks AM, Gornall AS, Larkins SA, Gardosi JO. Trisomies 18 and 13: trends in prevalence and prenatal diagnosis - population based study. Prenat Diagn. 2013 Aug; 33(8):742-50.