National Institute for Health Research

1. Full title of project:

HTA commissioned call (17/19): First trimester detailed ultrasound scan for the earlier detection of fetal anomalies: Clinical and/or cost-effectiveness of first trimester ultrasound screening for fetal anomalies: Is a prospective study an efficient investment?

2. Summary of Research:

Screening for fetal anomalies is routinely performed in the second trimester at 18-21 weeks of gestation. Recent data, including a meta-analysis by our group, suggest that screening for fetal anomalies in the first trimester is feasible, and will detect just over half of all prenatally detected anomalies (1). We have also shown a significant association between the sensitivity of first-trimester ultrasound and the use of an anatomical protocol for screening.

These findings suggest that first trimester anomaly screening has the potential to be a valuable addition to prenatal care for all women. The aims of the project relate to screening for fetal anomalies in the first trimester using detailed ultrasound scanning:

1. To conduct a series of systematic reviews to inform protocol development: in particular to answer what anatomical protocol should be used; at what gestational age; using which method of scanning; what false positive rates are.
2. To undertake a survey of the current screening environment and impact on the National Institute for Health and Care Excellence (NICE) care pathway: we have identified four pathways of first trimester ultrasound used in the UK today and this nationwide survey of all maternity units will establish current practice; the choice of screening that women are offered; and what impact a suspected abnormality has in changing a woman's care from the standard NICE antenatal care pathway.
3. To perform an analysis of UK-based data currently held by the National Congenital Anomalies Disease Registry (NCARDRS – operating under the aegis of Public Health England) in order to determine whether UK NHS trusts currently performing a routine first trimester anomaly scan are able to provide their patients with an earlier diagnosis than those trusts which do not offer this service, what system factors are associated to allow this, and whether this has any impact on patient outcomes such as earlier timing of diagnostic genetic testing and earlier termination of pregnancy. As this will require special permissions and contracts with Public Health England, which can be time consuming, we will start this work as soon as possible.
4. To conduct a Delphi consensus procedure to develop a protocol for the technical and logistical aspects of first trimester anomaly screening: this will involve healthcare providers from across the UK including sonographers, midwives, obstetricians and fetal medicine experts.
5. To determine the acceptability of the early anomaly scan amongst women, partners and caregivers across the UK. This will include understanding the opinions of parents who are currently pregnant and also those who have had previous experiences of a pregnancy or child affected by a fetal congenital anomaly.
6. To conduct an economic analysis and value of information (VoI) study: we will develop a decision analytic model to estimate the expected costs and outcomes associated with current practice and with prospective first trimester anomaly screening protocols identified by the work described above. (It should be noted that as part of this we also planned a detailed scoping exercise with data held by the British Associations of Paediatric Surgeons on longer term healthcare for newborns with conditions requiring surgical correction; however, this was unable to yield economic data for ultimate use in the HE model). The model will be structured and populated using evidence from the systematic reviews; national survey; consensus procedure; and from supplementary reviews of the literature and expert elicitation as required. The model will identify the protocol most likely to be cost-effective and will be operationalised so as to facilitate a VoI analysis to determine if it is worth investing additional research resources and effort in a definitive randomised trial.
7. To draw together the findings and recommendations from the project, and, if appropriate, outline the design of plausible prospective studies or trials. The design aspects of plausible prospective studies will include population, outcome and sample size.

3. Background and Rationale:

Fetal congenital abnormalities occur in 2-5% of the fetal population (2, 3). The precise number is difficult to estimate as this value can only be based on live births and stillbirths that have undergone autopsy. As the overwhelming majority of fetuses that miscarry are not examined, the true prevalence of fetal structural abnormalities is impossible to determine. Amongst liveborn and stillborn infants and fetuses that underwent pregnancy termination, data from the European Surveillance of Congenital Anomalies register (EUROCAT) suggests a prevalence rate of 203.35 non-chromosomal anomalies per 10,000 births (95% C.I.: 201.73-204.98) (4).

Congenital anomalies represent a significant cause of fetal, neonatal, childhood and adult morbidity and mortality. In the UK (as in most developed countries) prenatal diagnosis of congenital anomalies is offered. Women in the UK are offered two routine ultrasound scans, as recommended by the National Screening Committee under the aegis of the NHS Fetal Anomaly Screening Programme (FASP) (5, 6).

The primary aims of the first (at 11-14 weeks of gestation) are to confirm viability; establish accurate gestational age from the measurement of fetal crown-rump length (CRL); identify multiple pregnancies (and in these determine chorionicity); and measure fetal nuchal translucency (NT) thickness, as part of the "Combined Screening test"(6, 7). This combines maternal age, serum free BHCG, PAPP-A and fetal NT in order to determine fetal risks for Trisomies 21,18 and 13; it offers a detection rate of approximately 85-90% for Down's Syndrome and other aneuploidies, with a false positive rate of 5% (8).

The second scan at 18-21 weeks of gestation aims mainly to detect congenital abnormalities and specifically anencephaly ; open spina bifida; cleft lip; diaphragmatic hernia; gastroschisis; exomphalos; serious cardiac anomalies; bilateral renal agenesis; lethal skeletal dysplasia and chromosomal anomalies (mainly Trisomy 18 and 13) (5).

Thus, anomaly detection is currently based on this second trimester anomaly scan. The national screening program is regulated by the National Screening Committee (UK NSC) and the NHS FASP. According to NICE (6), the goals are to identify lethal and major abnormalities causing disability or those, which may be amenable to intrauterine or postnatal therapeutic management (5). The option of pregnancy termination for major fetal anomalies is enshrined in UK law (9). After mid-gestation diagnosis of anomalies this involves medical induction of labour, with a fetocide procedure recommended when the gestational age exceeds 21 weeks. Many parents who reach the difficult decision of pregnancy termination due to a major fetal anomaly feel there are potential advantages to first trimester (surgical) pregnancy termination in terms of reduced psychological morbidity (10, 11).

So is earlier detection of anomalies feasible? Considerable advancements in ultrasound technology in image quality, resolution and signal processing have fuelled interest in this field; given that the majority of fetal organ development is complete by 10 weeks gestation, ultrasound has the potential to be a valuable tool for early fetal structural anomaly screening. While studies have shown that a significant proportion of major anomalies can be detected between 11-14 weeks of gestation in both low-risk and high-risk populations (1, 12-14), there are areas of uncertainty and also potential risks, in particular in relation to false positive diagnoses. There remains some controversy as to whether first trimester anomaly screening is a sensitive enough tool to be valuable for use in daily clinical practice. In addition, unlike the current second trimester anomaly scan, there remains little international consensus as to what should be included in this early anomaly screening, in terms of both the anatomical structures which should be visualized at this stage and the image views which should be obtained for effective screening. Moreover, the specific objectives and role of first trimester anomaly screening as a part of prenatal care, particularly in relation to its second trimester counterpart, also remain unclear. This is a critical point if the health care system is expected to fund first trimester anomaly screening as part of routine practice.

4. Evidence explaining why this research is needed now:

The landscape of ultrasound in the first trimester of pregnancy in screening for anomalies is described above. Evidence why this research is needed now includes changes in clinical practice and research findings. These suggest that the detection rates are now high enough to justify assessing the utility of such a screening

approach. In addition there are parental and societal concerns about the late diagnosis of fetal abnormalities (15-17); these have increased the focus in this area, including parliamentary questions relating to late pregnancy termination(18-20).

The increasing evidence supporting the feasibility of detecting fetal structural abnormalities in the first trimester means that some - but not all - NHS hospitals have been undertaking ultrasound for detailed anatomical assessment in the first trimester and so there is lack of equity and access to care around the country. In addition, private providers offer such ultrasound scans and when problems are identified attendance in the NHS for the subsequent management of findings is common.

There is, therefore, ad hoc screening at present with very little evidence regarding the balance of risks and benefits. At the same time there are a number of uncertainties around how and when to screen; what false positive rates are; how to manage the findings; and questions about the cost, feasibility and acceptability.

In the light of these uncertainties, literature reviews and consensus, including with experts in fetal screening, and cost analyses are required. Hence the primary aim of the current proposal is for a detailed, reasoned and quantitative assessment of the potential for benefit and harm in relation to early anomaly screening using ultrasound; and how future studies should be designed to explore this.

5. Aims and objectives:

The aims and objectives have been designed to respond to the commissioning brief.

Specific aims are aligned with the work packages described below:

Aim 1 : To conduct a series of systematic reviews to inform the protocol development

1.1 What anatomical protocol should be used?

1.2 What is the best gestational age to screen?

1.3 Is there a preferred method of scanning (transabdominal (TA) / transvaginal (TV))?

1.4 What specific anomalies are amenable to first trimester detection and what are the expected detection rates?

1.5 What are the false positive rates for these different conditions?

1.6 How should data on fetal abnormalities be reported or “counted”?

Aim 2: To understand the current screening environment and impact on NICE care pathways of first trimester anomaly screening

We will conduct a nationwide survey of all maternity units to establish screening protocols; where screening takes place (hospital, primary care, etc); whether first-trimester anatomy scanning is offered irrespective of choice for aneuploidy screening; and the impact of a suspected abnormality (change from the NICE antenatal care pathway).

Aim 3: To perform an analysis of UK-based data currently held by the National Congenital Anomalies Disease Registry

The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) collects data on congenital abnormalities and rare diseases, under the aegis of Public Health England (PHE). As part of their role, NCARDRS collects information regarding the prevalence, timing of diagnosis, and outcome of fetal anomaly diagnoses of affected pregnancies across England (reporting to NCARDRS is a requirement for all trusts in England since 2017). We will request access to this data and perform an analysis to determine how the screening protocols followed by individual NHS trusts across England (ascertained in aim 2/WP 2) impact the timing of fetal congenital anomaly diagnosis, fetal genetic testing and termination of pregnancy in England.

Aim 4: To develop a protocol for the first trimester scan using a consensus procedure.

This will be based on recommended methodology, devised by experts in the field and lay representatives, including determining the acceptability of the early anomaly scan. Once the protocol is defined, we will propose auditable standards and quality assurance measures for first trimester anomaly screening.

Aim 5. Understanding parental opinions around first trimester anomaly screening

This will involve use of a validated questionnaire to understand parental attitudes around anomaly screening and to understand the acceptability of a first trimester anomaly screening programme to both parents who are currently pregnant and considered at low-risk for fetal anomalies and to parents with previous experiences of fetal anomalies in pregnancy.

Aim 6. Economic and VOI analysis

4.1 Using outputs from Aims 1, 2 and 3 we will develop an economic model to simulate and compare the costs and outcomes of the proposed protocols for first trimester fetal anomaly screening, with those of current practice. Incremental analysis will be used to explore the cost-effectiveness of protocols being compared.

4.2 The economic model will be probabilistic to facilitate VoI analysis. We will calculate the expected value of perfect information (EVPI) and partial perfect information (EVPPI) to determine whether there is economic value in undertaking additional future research. If findings are positive, we will explore the expected value of sample information (EVSI), expected costs, and the expected net gain of sampling (ENGS) for various trial designs and sample sizes.

Aim 7: To determine the final study design (if appropriate).

This will include designing plausible prospective studies and re-running the VoI analysis to predict the expected net gain of sampling (ENGS). Where appropriate, this will include identification of the most efficient sample size for such studies, the range of sample sizes yielding a positive ENGS, and comparison with the sample size yielded from a traditional power calculation.

6. Research Plan:

The background and other details are given above. This section describes the proposed work packages:

WP 1: Conducting a series of systematic reviews to inform the protocol development

All reviews will use the approach of the Cochrane Collaboration's Handbook for Diagnostic Test Accuracy Reviews [http://srdta.cochrane.org/handbook-dta-reviews]. The search strategy will be broadly similar to a recent systematic review and meta-analysis conducted by the lead applicants (1). With support from professional information specialist (Roberts), we will search on-line databases, including, but not limited to, Medline, Embase, CINAHL, Cochrane & Web of Science. Searches will be conducted using both MeSH terms and key words (with appropriate truncations to allow variants, e.g. ultraso* to cover ultrasound, ultrasonic, ultrasonographic etc). We will also use citations of key studies, and review reference lists of relevant papers. Titles and abstracts of all papers will be reviewed by two researchers. Candidate articles will be identified and a full copy obtained and reviewed; relevant translations will be obtained by overseas colleagues where feasible, or translation services available at Oxford.

The internal validity of studies will be assessed using the QUADAS-2 tool (21); in relation to bias, sensitivity analyses, based on stratification by study quality, will then be undertaken to assess the results in sub-groups of higher quality studies.We plan to use a range of approaches for the meta-analysis. We will use the 2x2 tables from each study and assess diagnostic odds ratios (these are widely used and have some useful properties, in particular that they are the ratio of the positive and the negative likelihood ratios). A bivariate regression approach will be used to arrive at summary estimates of sensitivity and specificity. We will also use the closely related hierarchical methods to generate summary ROC curves.

Results will be pooled using a random effects meta-analysis model, due to likely heterogeneity between studies. Formal testing for heterogeneity in the meta-analysis will be undertaken and if there is evidence of significant heterogeneity, the causes will be explored using meta-regression. Heterogeneity will be quantified

using I2 and causes of heterogeneity will be explored using meta-regression, with study design characteristics as the independent variable and deviation from the summary odds ratio as the dependent variable. Publication bias will be assessed by quantitative assessment of funnel plot asymmetry. In addition, screening performance will be assessed using positive and negative likelihood ratios, sensitivity and specificity, and positive and negative predictive values.

Using this methodology we will answer the following questions

1.1 What anatomical protocol should be used?

We have shown (1) that the sensitivity, in the first trimester, for the detection of major anomalies in unselected populations (19 studies, 115731 fetuses) is 46.10% (95% CI, 36.88–55.46%), representing 53.47% (95% CI, 43.42–63.37%) of all antenatally diagnosed ultrasound abnormalities. The detection rate for all abnormalities in unselected populations (14 studies, 97976 fetuses) was 32.35% (95% CI, 22.45–43.12%), while in high-risk populations (six studies, 2841 fetuses) it was 61.18% (95% CI, 37.71–82.19%). There was significant association (P<0.001) between the sensitivity of first-trimester ultrasound and the use of an anatomical protocol for screening, with a trend suggesting that the more detailed the protocol, the greater the detection rate.

As part of the preparation for this proposal we have already conducted a systematic review of all available screening protocols (Table 1).

Table 1: Currently available screening protocols: summary table

Anatomical Structure	Structure Required to be Visualized	Plane of Visualization	Supporting Protocols
Skull/Brain	Cranial ossification (contour/shape)	Transverse	14, 22-25
		Transverse + Coronal	26, 27
		Longitudinal	28
		No plane specified	29-44
	Choroid plexus filling lateral ventricles (butterfly sign)	Transverse	14, 22-28, 33
		No plane specified	31, 32, 34-40, 42, 43
	Cerebral peduncles	Transverse	23
	Thalamus	Transverse	27
		Mid-Sagittal	33
		No plane specified	42
	Interhemispheric fissure/falx	Transverse	14, 22, 24-26, 28, 30, 32
		No plane specified	29, 33-35, 37, 39, 40, 42, 44
	Posterior fossa	No plane specified	43
	Posterior fossa + demonstration of intracranial translucency	Mid-Sagittal	22, 23
		Transverse + Mid-Sagittal	33
	Intracranial Translucency	Longitudinal	28
	Cisterna magna	Transverse	24
		Transverse + Mid-Sagittal	33
	Cerebellum	Transverse	24
		No plane specified	27, 32, 34, 38, 40, 42, 43
Face	Orbits	Transverse	23, 24, 26, 28
		Coronal	27
		Transverse or Coronal	22
		No plane specified	25, 31-33, 37-39, 41-44
	Lenses	Transverse	24, 26
		No plane specified	39, 43
	Anterior palate	Transverse	23
		Mid-Sagittal	33

	Nasal bones	Mid-Sagittal	14, 26, 27, 33
		Sagittal	23, 24
		Longitudinal	28
		No plane specified	31, 34, 37, 38, 43
	Correct position of mandible	Mid-Sagittal	26
		Transverse + Sagittal	24
		Transverse or Coronal	22
		No plane specified	27, 33, 41, 42
	Correct position of maxillae	Transverse + Sagittal	24
		Transverse or Coronal	22
		No plane specified	41, 42
	Facial profile	Mid-Sagittal	22, 26, 27
		Sagittal	23, 24
		Longitudinal	28
		No plane specified	25, 31-33, 37-39, 41
	Ears	No plane specified	43
	Retronasal triangle	Coronal	23, 28, 33
	Upper and/or lower lip	Coronal	24, 26
		No plane specified	22, 25, 28, 41, 43
Spine	Presence/regularity of vertebrae from cervical to sacral regions	Longitudinal	14, 23, 25, 28, 36
		Longitudinal + Transverse	22, 26, 27, 38, 40-42
		Sagittal + Coronal + Transverse	24
		No plane specified	32, 33, 39
	Intact, continuous overlying skin	Longitudinal	23, 25
		Longitudinal + Transverse	38, 40, 42
		Sagittal	26, 37
		No plane specified	24, 27, 33, 34, 39
Thorax/Chest	Shape of the thorax	Transverse	24
		No plane specified	25
	Lung fields	Transverse	22, 24, 26
		No plane specified	25, 27, 31-33, 35, 43
	Diaphragmatic continuity	Longitudinal	28
		No plane specified	22, 24-27, 31-35, 41, 42, 45
Heart	Situs evaluation	Transverse	22, 23, 43
		Longitudinal	28
		No plane specified	26, 27, 30, 33, 34, 36, 38, 40, 41
	Heart area in relation to chest	Transverse	23
	Cardiac axis	Transverse	26, 34, 38, 40, 43
		No plane specified	29
	Four-Chamber view (with AV valve offsetting)	Transverse	14, 22-24, 26, 43
		Longitudinal	28
		No plane specified	25, 27, 32-42, 44, 45
	Outflow tracts (pulmonary artery, aorta, SVC – 3 vessel view)	Transverse	23, 24, 43
		Longitudinal	28
		No plane specified	22, 27, 33, 37-39, 41
	Aortic Arch	No plane specified	40, 43
	Fetal heart rate	No plane specified	26, 27, 32, 34, 38, 40
Abdomen	Presence of stomach in left quadrant	Transverse + Sagittal	14, 22
		Transverse + Coronal	26
		Transverse	24
		Longitudinal	28
		No plane specified	23, 25, 27, 29, 30, 32-44
	Presence of bladder in fetal pelvis	Transverse + Sagittal	14, 22, 24
		No plane specified	23, 25-27, 29-34, 36-45

	Bilateral presence of kidneys	Coronal + Transverse	24
		Coronal	26, 27
		No plane specified	22, 23, 31-33, 35-43, 45
	Intact abdominal wall with demonstrated umbilical cord insertion	Transverse + Sagittal	14, 22
		Transverse	28
		No plane specified	23-27, 30-44
	Bowel echogenicity	No plane specified	23, 24, 43, 45
	Gallbladder	No plane specified	43
	External genitalia	No plane specified	32
	Bifurcation of portal vein	Transverse	24
Limbs	Symmetry and adequate views of long bones of all 4 limbs	No plane specified	22-27, 29-45
		Longitudinal	28
		Transverse + sagittal	14
	Bilateral feet visible with correct orientation	Transverse + sagittal	14
		Longitudinal	28
		No plane specified	22-27, 31, 33-35, 37, 39, 41-45
	Bilateral toes visible	No plane specified	23, 24, 32, 37, 39
	Bilateral hands visible with correct orientation	Transverse + sagittal	14
		Longitudinal	28
		No plane specified	22-27, 31, 33-35, 37, 39, 41-45
	Bilateral fingers visible	No plane specified	23, 24, 29, 32, 37, 39

Notes: excluded assessment of soft markers (eg. NT), Doppler investigations and fetal biometry.

As part of this study we will undertake a wide scoping and consulting exercise to inform a consensus meeting in order to determine the best ultrasound protocol to use (see WP 2). This is important because detection rates for different types of anomalies differ significantly (see Table 2).

Table 2: Classification of fetal anomaly detection in the first trimester, based on (13, 14, 27, 28).

Anomalies Considered to be Nearly Always Detectable (approx. 90-100%)	**Anomalies Considered Potentially Detectable (approx. 2-90%)**	**Anomalies Considered to be virtually undetectable (<2%)**
Acrania	Facial clefts	Corpus callosum agenesis
Anencephaly	Hydrocephalus	Bladder exstrophy
Alobar holoprosencephaly	Spina Bifida	Congenital cystic adenomatoid malformation
Encephalocele	Skeletal Dysplasias	Extralobar sequestration
Ectopia cordis	Arthrogryposis	Cerebellar hypoplasia
Exomphalos	Limb reduction	Duodenal atresi
Gastroschisis	Polydactyly	Anal atresia
Megacystis	Septal Defect	Bowel obstruction
Body stalk anomaly	Transposition of the Great Arteries	Duplex kidneys
	Double-outlet right ventricle	Hydronephrosis
	Aortic Coarctation	Ovarian cyst
	Hypoplastic left heart syndrome	Fetal tumours (nasopharyngeal, cardiac and sacrococcygeal)
	Valvular Disease	
	Multicystic Kidneys	
	Dandy-Walker Syndrome	

1.2 What us the best gestational age to screen?

Studies suggest that anatomical visualization improves significantly with increasing gestational age between 11 and 14 weeks, impacting in particular on the examination of the fetal heart and kidneys. The most recent and largest studies that address this issue (see Table 3) suggest that later screening has advantages both for overall anatomical assessment; and for detection of specific anatomical views.

Table 3: Effect of gestational age / fetal size on detection rates for fetal anomalies

Souka et al. (46):				
CRL	45-54mm	55-64mm	65-74mm	75-82mm

(GA)	(11^{+0}-11^{+6})	(12^{+0}-12^{+5})	(12^{+6}-13^{+3})	(13^{+4}-14^{+0})
Complete anatomy excl.cardiac exam	65%	84%	93%	96%
Complete anatomy incl. cardiac exam	22%	43%	56%	67%
4-Chamber view	67%	86%	94%	98%
3-Vessel view	25%	46%	58%	67%
Luchi et al. (47):				
4-Chamber view	87%	98%	100%	
3-Vessel view	64%	86%	94%	
Kidneys	36%	62%	89%	
Cerebellum	12%	66%	87%	

However, this improved detection rate with advancing gestation needs to be balanced against the later detection, and the impact on screening for chromosomal anomalies. We will conduct a sensitivity analysis of screening performance for anatomical defects by gestational age and use a model to assess optimal gestational age for the detection of both anatomical and chromosomal abnormalities for those women who opt to screen for both.

1.3 Is there a preferred method of scanning (transabdominal (TA) / transvaginal (TV))?

Most reported studies use a combination of TA and TV ultrasound. Findings from studies evaluating fetal organ detection suggest that optimal visualization rates are obtained with a combination of TA and TV ultrasound(42). For TA, raised BMI, fibroids or retroversion of the uterus will decrease image quality (37, 42, 48). In contrast, TV ultrasound provides much higher resolution, but has the disadvantage of limited probe manoeuvrability (48) and reduced acceptability (37, 49). A detailed comparison between sensitivities from studies using one of the three methods (TA, TV or combination of both) will be undertaken.

1.4 What specific anomalies are amenable to first trimester detection and at what detection rates?

Some conditions seem nearly always detectable in the first trimester, others never identifiable and some can be diagnosed, depending on maternal, fetal, sonographer and equipment factors (13, 14, 27, 28). Thus, first-trimester anomaly screening may need to be considered as an adjunct, as opposed to a replacement of ultrasound examination at later gestational ages. Thus expectations and future objectives for first-trimester anomaly screening must be tailored to the type of anomalies amenable to reliable detection at this gestational age. At present, the literature has little data focused on the sensitivity of ultrasound at 12 weeks of gestation for individual anomalies. This will need to be further explored in order to identify which conditions should be specifically targeted by a national first trimester anomaly screening program.

1.5 What are the false positive rates for these different conditions?

It must be highlighted that the majority of existing studies do not report false positive rates. One of the inevitable consequences of first trimester screening is the offer of early termination of pregnancy when major anomalies are seen. There is a self-evident concern regarding offering termination of pregnancy after first trimester anomaly screening without a full understanding of a false positive diagnosis. It is not always easy to work out what a false positive is, as anomalies evolve: for example, a significant proportion of megacystis or bowel-only exomphalos resolve spontaneously with advancing gestation. Hence, it is critical not only to understand the false positive rate in first trimester screening, but also what types of anomalies are most likely to resolve spontaneously.

1.6 How should data on fetal abnormalities be reported or "counted"?

This is not straightforward as the number of structural abnormalities is reported in various ways in different studies. For example, studies variably report the number of fetuses affected by one or more anomalies in the numerator, with normal fetuses in the denominator; but as fetal anomalies may be multiple, other authors count the number of fetal anomalies. Even what constitutes 'one detected structural abnormality' is not defined uniformly: for example, bilateral defects (such as bilateral renal agenesis) are counted variably as one or two individual structural anomalies. Secondly, fetuses diagnosed with a syndrome, based on the findings of multiple malformations on ultrasound, are variably reported as having one anomaly (the syndrome) or several anomalies (the constituent defects). Thirdly, in several studies, a single fetus may be attributed to having

multiple anomalies within one organ system (eg. 'multiple skeletal abnormalities'). In this case, the fetus could be considered to have one structural ("a skeletal") abnormality. Finally, soft markers for fetal aneuploidy (including increased NT and absent nasal bone) are sometimes included as anomalies; these will be excluded in this review as they do not constitute fetal defects per se.

As can be seen there are several subtleties and uncertainties that require definitions and proposals will be made on the basis of literature review and consensus, including with the experts in fetal screening.

WP 2. Survey of the current screening environment and impact on NICE care pathway

A national scoping exercise has identified four broad categories of routine first trimester ultrasound scans practiced in the UK:

1. Basic first trimester ultrasound: Confirmation that the fetus is alive, accurate dating by measurement of fetal CRL and detection of multiple pregnancy

2. Basic first trimester ultrasound and measurement of fetal nuchal translucency (NT): as above, PLUS screening for chromosomal abnormalities usually in conjunction with first trimester maternal serum biochemistry

3. Basic first trimester ultrasound, measurement of NT and assessment of the fetal anatomy: as above, PLUS purposeful assessment of fetal anatomy with the aim of diagnosing major fetal abnormalities

4. Detailed fetal first trimester anatomical ultrasound: often reserved for targeted screening due to a previous abnormality or other risk factor, this is routinely undertaken in some UK centres and includes more detailed anatomical assessment.

We will conduct a nationwide survey of all maternity units to establish

- Screening protocols

- Where screening takes place (hospital, primary care, etc.)

- Whether first-trimester anatomy scanning is offered irrespective of choice for aneuploidy screening

- The impact of suspected abnormality (change from the NICE antenatal care pathway)

Management of pregnancies which screen positive are not covered in current UK clinical guidelines. We will combine this information with a systematic literature review to create possible management pathways.

WP 3: Consensus procedure to develop a protocol for the first trimester scan

In preparation for this step the detailed systematic reviews and survey results will be available. Given the large range of protocols available, the limitations from existing screening studies described and the need to create such a protocol in the light of the ultrasound scanning resource available, it is unlikely that guidance can be established based on research-based evidence alone. In order to capture interpretation of experts in the field, we will use the background protocol information to undertake a consensus procedure in order to unify individual opinions into a group consensus. This will consist of our expert panel as well as other experts in the field and lay representatives. Web-based tools (REDCap) will be used to gather the views of a range of professional stakeholders on the elements of the screening test, design of a screening trial, and the feasibility of population screening. Further methodological details regarding question development, selection and size of participant pool, analysis of iteration output and definitions of group consensus will be determined as part of the study and with adherence to recommendations from HTA guidance on consensus development methodology) (50).

A series of structured statements developed on the basis of our extensive literature review, which will require ranking of significance using a Likert scale. These results will be summarized using measures of central tendencies and levels of dispersion; statements will be fed back to participants with increasing detail over multiple rounds. With each iteration, the participants will be allowed to revise their opinion in light of the group feedback until relative consensus has been reached.

The issues we expect to address using this methodology include optimal gestational age for first trimester anomaly screening, anomalies which should be targeted, details of screening protocols including definition of

standard anatomical views and time to be allocated for screening. The issue of how first trimester screening should be developed in relation to its current second trimester counterpart will be considered. Discussions regarding the usefulness of developing a basic first trimester screening protocol alongside a more detailed protocol and the clinical situations where these might be beneficial will also be undertaken.

Finally, it is critical that alongside a standardised protocol, we have auditable standards combined with a quality assurance program for first trimester anomaly screening. This will be a key to the initiation and maintenance of a standardised and reproducible system – whether as part of a trial or implementation of first trimester anomaly screening across the UK.

There are no current quality control systems described in the literature that are specific to first trimester anomaly screening, but our group has developed score-based quality assessment tools for the purposes of sonographer teaching and for monitoring the skills of existing sonographers in the second trimester as well as for the measurement of fetal CRL and NT (51-53). We are currently evaluating the feasibility and reliability of using such a system for first trimester anomaly screening, and will publish such a scoring system as part of this project.

WP 4: Economic analysis and value of information (VoI)

4.1. Economic analysis of screening and intervention protocols

After reviewing the health economic literature we will identify the most appropriate modelling framework, model structure, key study parameters and potential measures of outcome. Some of the co-applicants (including the PI) are currently constructing a model to estimate the cost-effectiveness of late-pregnancy ultrasound screening (HTA 15/105/01). Whilst there is obvious overlap, there are also substantially different issues involved in the early screening model (see below), negating simple duplication. However, we anticipate being able to use some of the parts of the outline model as a starting point.

The model we develop will estimate the costs and outcomes of first trimester anomaly screening protocols and of current practice. An NHS and social services cost perspective will be taken in the first instance, and a wider societal perspective considered should data permit. The potential outcomes of first trimester anomaly screening are complex, multifaceted, and ethically sensitive with implications for both parents and infant. Specifically, a standard 'cost per QALY' approach might not be appropriate in this context as a decision to terminate a pregnancy will lead to a lifetime loss of QALYs, yet may be the desired maternal / couple's outcome. We are acutely aware of the sensitivities involved and so our analysis will acknowledge this and, in line with other studies in the field, we will seek to report separate outcomes using a cost-consequence framework (54). Specifically, we will explore outcomes from the perspectives of the mother, infant and (if data permit) both parents.

We hypothesise that earlier detection of a major anomaly could alter women's preferences for continuing a pregnancy and so will construct our model to simulate the impact on the pregnancy termination rate and the number of babies born with a major anomaly. An increased risk of miscarriage from invasive testing following a false positive early screen will also be considered. Equally important is the impact on parents. The psychological sequelae of terminating a pregnancy for a major anomaly are significant and any additional burden should be reflected (10, 11, 55, 56). Furthermore, the potential for false positive results with early screening and the associated anxiety and morbidity from additional invasive testing must also be considered. In contrast, earlier anomaly detection and intervention may avert some of the distress, and may avoid the additional pressures that parents feel to reach a decision about their pregnancy before the 24-week legal termination limit (55). Also, and should a termination be chosen, an earlier procedure may expose women to less physical harm than a later procedure. We plan to explore the likely net impact of all of these consequences upon maternal and parental utility during the pregnancy.

We foresee a need to compare variants of protocols (with different anatomical specifications / screening modalities and personnel / interventional pathways) and expect to operationalise these as alternative comparators within a decision tree model covering each of the three trimesters to birth. Within each trimester, the model will be structured for any anomaly screening results, related prevalence and sensitivity/specificity and intervention pathways, and will be populated with data on associated event

probabilities, costs, and parental and infant payoffs. Separate outcomes will be presented using the decision tree and will include births with a major anomaly, and maternal and parental utility during the pregnancy (expressed as quality adjusted life years (QALYs)). At this stage, we anticipate a paucity of data on the false positive rate (and hence specificity) of tests. The statistics will also vary by anomaly. Where data are not forthcoming we will seek expert opinion using a structured elicitation technique (e.g. SHELF) (57).

If the hypotheses above are correct, the implications of first trimester anomaly screening will extend beyond the pregnancy. For example, there may be long term cost-savings for the NHS and social services as well as a reduction in the parental burden of caring for a child born with a major anomaly. However, the notion that these benefits are realised through an increase in the number of pregnancies being terminated is ethically challenging. Indeed, the likely preferences of society for such a program are unclear. This in turn raises questions about the use of conventional cost-utility analyses whereby results are interpreted within the context of society's valuation of a QALY (54, 58). Although our primary approach will take the form of a cost-consequence analysis, we will also calculate incremental cost-effectiveness ratios, but would emphasise that in the light of the sensitivities discussed above, that these should be interpreted with caution.

Protocol alternatives and input parameters for the model will be informed by WPs 1, 2, and 3 as well as by supplementary literature searching and expert elicitation. We will utilise the planned national survey to elicit information on pregnancy termination rates with and without first trimester anomaly screening and will interrogate the Department of Health's termination statistics. Cost data will be sourced from administrative datasets, hospital finance departments, and the published literature. Model parameters will be entered as distributions and the resulting simulated costs and outcomes of each alternative will be compared to rule out dominated and extended dominated protocols. Incremental cost-effectiveness ratios (and/or net health/monetary benefit) will be computed for the remaining protocols and a VoI analysis conducted. These analyses will be conducted for various outcomes (including the number of births with an anomaly, and maternal quality adjusted life years) so as to make clear the social value judgements that arise when outcomes for different affected parties are considered. As a secondary analysis, we will also perform these works using the long-term cost and QALY framework, if viable.

Our intention will be to use the individual cost-effectiveness outcomes modelled (for example cost per live births with an anomaly averted or cost per maternal QALYs gained) in separate VoI analyses, which will also provide evidence regarding any recommendation about subsequent research. The cost-consequence approach to the economic analysis will allow the potential implications of the policy for the various affected parties (the babies, parents, and wider society) to be fully quantified and reported separately.

4.2. Value of Information (VoI) analysis

Using the model's facility for probabilistic sensitivity analysis, we will calculate the expected value of perfect information (EVPI) and partial perfect information (EVPPI) and if either suggests value from future research, we will explore the expected value of sample information (EVSI), expected costs, and the expected net gain of sampling (ENGS) for various trial designs and sample sizes.

VoI analysis is complicated by the inability to calculate a single meaningful incremental cost per QALY gained from the screening intervention. We will, therefore, conduct these from the outcome perspectives of the mother, both parents, and if appropriate, from society too. The exact specification will be determined prior to analysis, but may, for example, in the case of the mother and parental perspectives, lead to the outcome being dichotomised into 'desirable' or 'undesirable', where a desirable outcome is one where a fetus is either carried to term or terminated in accordance with the wishes of the parent(s). Thus, the driver for 'undesirable' outcomes will be a function only of the false positive and negative rate of the screening test, thereby avoiding any social value judgements associated with the decision itself. The EVSI will then be interpreted as the expected gain in 'desirable' outcomes from additional information yielded from a trial. The cost and EVSI from alternative trial designs can then be compared in stepwise manner, excluding dominated and extended dominated options.

WP 5: Determining the final study design

We will draw together the findings and recommendations from the project, and, if appropriate, outline the design of plausible prospective studies. The VoI analysis will be rerun to predict the expected net gain of sampling (ENGS) of these. Where appropriate, this will include identifying the most efficient sample size for such studies, the range of sample sizes yielding a positive ENGS, and comparisons with the sample size yielded from a traditional power calculation.

If a study is deemed efficient, we will develop the relevant parameters. Possible designs include a prospective cohort screening study with ascertainment of outcomes; here we would explore whether it is acceptable to women and caregivers not to reveal those anomalies that are associated with a high false positive rate or thought to resolve spontaneously in a large number of cases, e.g. small exomphalos or megacystis of <15mm diameter (14, 59).

It would also be possible to undertake a randomised trial with women randomised to having or not having the first trimester anomaly screening test. All women in the screened arm who have a positive first-level result would then have further detailed assessment.

We will also consider the possibility of randomising at hospital level, e.g. using a cluster or stepped wedge RCT. Finally, we would also consider the potential use of an adaptive trial design. The team includes a senior statistician and leading trialists (Linsell , Thorton, Alfirevic, Jusczak), who have extensive experience of different methodological approaches.

Details of candidate study designs will be defined in specifically designed workshops with the PPV

group. Particular aspects will be acceptability of:

- different study designs;
- reporting only major anatomical landmarks and blinded research elements for more detailed assessment;
- non-disclosure of suspected (but unconfirmed) anomalies;
- consent procedure.

The impact of declining or accepting screening for chromosomal abnormalities, including cell-free DNA screening, will be assessed in the context of anomaly screening. This is important as some anomalies (e.g. exomphalos, megacystis, holoprosencephaly) are strongly associated with trisomy 13 and 18 (60, 61). Hence, detecting such anomalies may itself increase the chances of a pregnancy being affected by such a trisomy.

WP 6: Analysis of UK-based data currently held by the National Congenital Anomalies Disease Registry

This work package is a new addition to version 9 of the protocol and was developed in response to findings from the work undertaken in WP1 and WP2. The nationwide survey of current ultrasound practice in England has shown that at present 75% of NHS Trusts routinely assess fetal anatomy in the first trimester, despite the absence of national policy. However, there is significant variation in practice seen between trusts regarding the anatomical structures evaluated in the first trimester, the anatomical image views obtained by sonographers routinely, the amount of time spent on scanning, and the training provided to sonographers.

Given that many trusts are already performing some form of first trimester anomaly scan, it is now feasible to use UK specific data (collected routinely by NCARDRS) from these ultrasound units in order to model the impact of the first trimester anomaly scan on the timing of fetal anomaly diagnoses, the timing of investigations (such as CVS/amniocentesis) and the timing of termination of pregnancy. Ultimately, this should allow us to determine whether trusts performing a routine first trimester anomaly scan are able to provide their patients with an earlier diagnosis than those trusts which do not offer this service, what system factors are associated to allow this, and whether this has any impact on patient outcomes. This data will be used in conjunction with the international literature-based data collected in WP1 to develop a more accurate and precise health economics model in WP4.

This work involves a collaboration between our group, NCARDRS and PHE. It will involve two members (AP and research fellow, JK) to obtain honorary research contracts from PHE and for the work to be formally approved by research ethics committee.

WP 7: Determining the acceptability of the early anomaly scan amongst women and their partners

This work package is a new addition to version 9 of the protocol, although a large part of this work was previously included as part of WP3. This was done partly as the original protocol had planned for in person focus groups and workshops to be conducted in order to understand parent experiences of fetal anomaly screening, to explore whether women who decline or accept screening for chromosomal abnormalities (commonly the current focus of first trimester ultrasound) would decline or accept first trimester anomaly screening and to determine the acceptability of the early anomaly scans amongst parents. Given the logistical difficulties presented by the Covid pandemic, we have introduced WP7 in an effort to allow parental opinions to inform our research and the design of the trial intervention (WP5).

WP7 will involve the distribution of a validated, prospective survey to two distinct participant cohorts in an effort to understand parental attitudes to a future first trimester anomaly scan.

Cohort A:

This will involve distribution of the survey to women who are currently pregnant and their partners. Women and their partners will be approached to participate in the study upon their arrival for routine NHS obstetric ultrasound screening at one of ten participating units across England and Wales.

Cohort B:

This will involve distribution of the survey to parents who have previously experienced a screen-positive result following ultrasound screening for fetal anomalies in pregnancy, or who have experience of a child affected by a fetal anomaly. We will aim to target those who proceeded with termination of pregnancy and those who continued with the intent of live birth. We will also aim to include parents who received a false positive screening result. Women and their partners will be approached to participate in the study one of several national charities collaborating with this project, which including Antenatal Results and Choices (ARC) and Spina Bifida, Hydrocephalus, Information, Networking, Equality (SHINE).

7. Health technologies being assessed:

The health technology being assessed is fetal ultrasound assessment in the late first trimester of pregnancy. Considerable advancements in ultrasound technology in image quality, resolution and signal processing have fuelled interest in this field. Given that the majority of fetal organ development is complete by 10 weeks of gestation, ultrasound has the potential to be a valuable tool for early fetal structural anomaly screening.

Ultrasound is already established as a test in the first trimester of pregnancy (to diagnose miscarriage, multiple pregnancy, and major chromosomal abnormalities) and in mid-gestation (principally to screen for congenital anomalies) (5, 6).

However, ultrasound is currently only used selectively for anomaly detection in the first trimester. The current project aims to assess the potential, on the basis of all existing evidence, for adding fetal anomaly detection to the first ultrasound scan for all pregnant women. The advantages of earlier diagnosis need to be balanced against lower sensitivity (in particular cardiac defects and spina bifida); false positive rates; and cost. The first can be overcome by maintaining the second scan; the second and third have been under-studied in the existing literature.

Although the focus is on ultrasound, the way this fits into the overall screening “landscape” will be assessed; thus the impact of changing rates of accepting / declining screening for chromosomal abnormalities, including cell-free DNA screening, will be evaluated.

8. Design and theoretical/conceptual framework:

The project involves multiple study designs. First, it will involve systematic literature search and meta-analysis of data from studies that assess the detection rates for fetal anomalies using ultrasound examinations in the first trimester. Second, it will involve sensitivity analyses of studies that describe the effect of factors in detection rates. Third, survey results of current practice will allow the feasibility of implementation of protocol-driven screening in the UK, and consensus will be developed to define the protocol for such screening. This will also include objective image criteria that currently do not exist: for example, in the second trimester image criteria determine which aspects of the head should be seen when circumference is

measured; this allows optimal imaging and the quality of image acquisition to be audited. Similar image criteria need to be determined for the first trimester (5). Fourth, decision analytic modelling will be employed to determine whether a program of screening and intervention, with performance as estimated on the above evidence synthesis, would be cost effective when compared with other medical expenditure in the UK. Fifth, it will involve a value of information analysis that assesses the economic case for performing a research study, balancing the utility of the information with the costs of conducting the study. Finally, all the elements above will be considered and a protocol for testing the effect of universal screening using ultrasound drafted.

9. Target population:

The current application is in response to a commissioned call, hence the target population was determined in the brief. The target population will be all pregnant women in the UK, who are currently offered two routine ultrasound scans. The primary aims of the first (at 11-14 weeks of gestation) are to confirm viability; establish accurate gestational age from the measurement of fetal CRL; identify multiple pregnancies (and in these determine chorionicity); and measure fetal NT thickness, as part of the "Combined Screening test" for Trisomies 21,18 and 13. The second scan, at 18-21 weeks, aims mainly to detect congenital abnormalities and specifically for the detection of anencephaly ; open spina bifida; cleft lip; diaphragmatic hernia; gastroschisis; exomphalos; serious cardiac anomalies; bilateral renal agenesis; lethal skeletal dysplasia and chromosomal anomalies (mainly Trisomy 18 and 13)(5, 6).

The choice of offering the scan to all women is in keeping with national screening policy and the fact that, although women at high risk of fetal abnormality have an increased chance of fetal anomalies, overall the majority of fetal anomalies occur in low-risk women (62, 63). The timing of screening, i.e. in early pregnancy, is purposeful, and is informed in part by thinking about the likely nature of earlier pregnancy termination, which may mitigate the risks of an adverse outcome (10, 11, 16, 17, 64).

It is also likely to be associated with higher satisfaction rates. Studies on the impact of prenatal congenital fetal anomaly diagnosis for parents suggest significant emotional and psychological distress, depression and anxiety after disclosure of results at both 6 week and 6 month follow-up (56). In addition, high levels of psychological distress are seen in women following pregnancy termination for fetal anomaly (65), but there are much greater levels of post-traumatic stress symptoms in women undergoing second trimester compared to first trimester termination (OR 9.3) at 6 weeks post procedure (10). In a longitudinal study with follow-up of up to 7 years (11) advanced gestational age at pregnancy termination was associated with higher levels of grief; in contrast, post-traumatic stress and long-term psychological morbidity were rare in women undergoing termination prior to 14 weeks of gestation.

Nevertheless, the advantages of earlier diagnosis need to be balanced against lower sensitivity (in particular cardiac defects and spina bifida); false positive rates; and cost. The first can be overcome by maintaining the second scan; the second and third have been under-studied in the existing literature.

The focus of the analysis – all (unselected) pregnant women in early pregnancy – is informed by evidence, screening policy a potential beneficial net effect of earlier screening.

10. Inclusion/Exclusion Criteria:

All pregnant women will be eligible. The hypothetical care pathway to be evaluated is one where all pregnant women are still offered two routine scans, but where anomaly detection would not be assessed only at the second scan, but also at the first. We will define care pathways for women who do and those who do not wish to take up such screening.

No primary research will be undertaken; however, we will evaluate the potential contribution first trimester ultrasound might be able to play in the early detection of structural defects, based on what is known in studies; create a protocol-driven methodology for performing this scan, and conduct an economic analysis and a value of information study as described.

11. Setting/context:

The setting for the study is prenatal care of populations of mixed risk, which is shared between primary and secondary care. Data collection and analysis sare discussed in the respective sections above.

For search the strategy of data synthesis please see WP 1 in section **7. Research Plan**.

The context of the Health Economic Analysis merits specific mention. Putting all ethical aspects aside, health economists most frequently measure the health impact of a disease or intervention using Quality-Adjusted Life Years (QALYs); in fact this is a requirement for all technology assessment submissions made to the National Institute for Health and Care Excellence in England. The basic premise behind the QALY is that when assessing the impact of a disease or intervention, the effect upon quality of life as well as quantity of life is considered. Quality of life is usually measured on a scale anchored at 0 and 1 - where a value of 1 signifies perfect health and a value of 0 signifies death/non-existence. These scores are then used to weight the number of life years lived. Assuming then, that severe health complications might carry a quality of life value of e.g. 0.5, then a child living with these complications for 20 years would accrue 10 QALYs (0.5 * 20). This is clearly inferior to a life in perfect health (20 QALYs): living with the complications would mean a loss of 10 QALYs compared to perfect health.

The question we must ask ourselves in the context of this study is how we can assess this in relation terminated pregnancies. In that case, the comparison would be a terminated pregnancy with associated 0 QALYs versus a child with complications over 20 years with associated 10 QALYs. Therefore, from a QALY perspective, termination of pregnancy would always result in a loss of QALYs when compared with a child with complications (unless living with complications resulted in negative QALYs over the 20 year span) even though this may have been at the wish of the mother or parents. How this translates into whether a detailed anomaly scan at first trimester has the potential to be cost-effective is something the project team and PPV group have thought about deeply.

Although the standard 'cost per QALY' methodology is the most frequently used approach to economic evaluation because it provides a common measure of outcomes and facilitates cross-intervention comparisons, in this instance it may not be appropriate for the reasons described above and in Section 7. In view of the fact that different parties stand to be affected by this policy, if it is adopted, we have proposed the use of a cost-consequence analysis, which by allowing a range of various outcomes to be considered (perhaps including the QALY), may be one way to answer such a controversial question and would allow policy makers to contextualise the results. The detailed description in WP 4 of section **7. Research plan** deals in more detail with the issues.

12. Sampling

A detailed description of this is given in the Research Plan section. Briefly, sampling of the literature will be undertaken using systematic review methodology to ensure that as far as possible all relevant publications are reviewed. In terms of sampling of participants for the consensus procedure, we have formed a very broad

13. Data collection:

A detailed description of sampling is given in section 7 (Research Plan). Briefly, data will be collected from systematic reviews and will result in candidate papers; a database will be created in EndNote (Thomson Reuters). Data from individual studies will be extracted and authors contacted where this is not possible from published results. For scoping opinions web-based tools (REDCap) will be used to gather the views of a range of professional stakeholders on the elements of the screening test, design of a screening trial, and the feasibility of population screening. The applicants include healthcare professionals from all areas of prenatal care. They are strategically positioned in, and have strong links with, relevant organisations, and this will ensure the feasibility of wide ranging sampling for scoping and consensus building (Antenatal Results and Choices (ARC); Tiny Tickers; Spina Bifida - Hydrocephalus - Information - Networking – Equality (SHINE); National Childbirth Trust; Royal College of Midwives; Royal College of Obstetricians and Gynaecologists; Society & College of Radiographers; National Screening Committee; British Medical Ultrasound Society; British

Maternal Fetal Medicine Society; International Society of Ultrasound in Obstetrics and Gynecology; Fetal Medicine Foundation, amongst others).

14. Data analysis:

A detailed description of this is given in 7. Research Plan. Extracted data from systematic reviews will be analysed using RevMan (66) software or STATA for more complex analysis such as metaregression, or where better random-effects estimators are required(67).

15. Dissemination and projected outputs:

Our dissemination plan reflects the ultimate purposes of this study, i.e. derive a protocol for the first trimester scan and estimate the value of continued research in the area, rather than inform policy directly. However, should our results suggest that no further research is worthwhile, the economic model will be used to inform policy and we will adjust our dissemination strategy accordingly.

15.1 Scientific publications

We anticipate a series of publications that address the different aims of the project. First, we anticipate that we will publish a series of systematic reviews as described in WP 1. Second, we will publish systematic reviews of management pathways that are not currently informed by an up-to-date systematic review. Third, we will publish a health economic analysis of the case for implementing a program of detailed early screening for fetal anomalies, using different levels of uncertainty in screening performance. Fourth, we will publish a value of information analysis, which informs the economic case for performing the trial. Finally, if applicable, we will publish an outline for an RCT, including an overview of the rationale for the approach developed.

15.2 Dissemination through our Patient and Public Voice group

We anticipate wide dissemination of the study through the PPV group that has committee to undertake this through the relevant charity websites, social media and local meetings.

15.3 Scientific presentations

The PI and co-PIs are all very active in local, national and international meetings where ultrasound screening is an area of interest. In addition, some of the applicants organise national and international conferences, courses and meetings. Hence, there would be a huge potential exposure of the work from this project to audiences in the UK and internationally.

The PI and co-PIs also have close links with the organisations that inform and lead clinical practice in the UK. For example Pandya is an advisor to the UK National Fetal Anomaly Screening Programme; Chudleigh is a senior member of the British Medical Ultrasound Society and author of several key prenatal screening policy documents; Smith was the senior author of the chapter on Prenatal Screening in the Chief Medical Officer's 2014 Annual Report; Papageorghiou and Smith are current members of the RCOG Research Committee and Thilaganathan is a Council member of the RCOG; Nicolaides is the Director of the Fetal Medicine Foundation; Alfirevic is the chair of the Clinical Standards Committee of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), and co-author of the international first trimester screening guidelines of ISUOG; while Papageorghiou is the Honorary Secretary of the same organisation. Hence, although high quality publications of original research are a key element of the dissemination policy, the applicants are well placed to ensure wider dissemination through multiple channels.

16. Plan of investigation and timetable:

Work Package	2018	2019				2020				2021				2022			
	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
WP1: Systematic Reviews & Meta-Analyses															update	update	
WP2: Nationwide Survey of Current Screening Environment																	
WP3: Delphi Consensus Procedure																	
WP4: Economic Model Development																	
WP5: Deliberations and Consensus on Possible Future Trial Design																	
WP5: Shaping the Final Study & Protocol Drafting																	
WP6: Collaboration with NCARDRS						permissions	permissions	permissions	permissions								
WP7: Acceptability of the early anomaly scan																	
Project Write-Up & Dissemination of Results																	

Work disrupted due to COVID-19

17. Project management

The Study Steering Group (SSG) will include all co-applicants. Additional meetings will be held by the PPV group; and hospital management group, and feed into the groups. The chair of each will also be represented on the SSG. The day to day management of the study will be the remit of the coordinating centre at Oxford (AP, Research associate, ORA, HC), while alternate month face-to-face meetings will be facilitated with the health economics group at Cambridge. Finally, the independent advisory committee will oversee the smooth running of the study and provide expertise on ensuring progress of research and dissemination.

All applicants are highly engaged in the proposal. Collaborative management of the project when active will be through (i) teleconferences (TC) every 2 weeks, (ii) face to face meetings every quarter. In addition, consensus meetings will be held according to the timetable. Written minutes will be circulated by email following both TCs and face to face meetings, and will include a summary of action points. Each subsequent TC or face to face meeting will assess progress on the action points from the preceding meeting. Progress towards the overall aims of the project will be assessed in relation to the Gantt chart, and achievement of milestones.

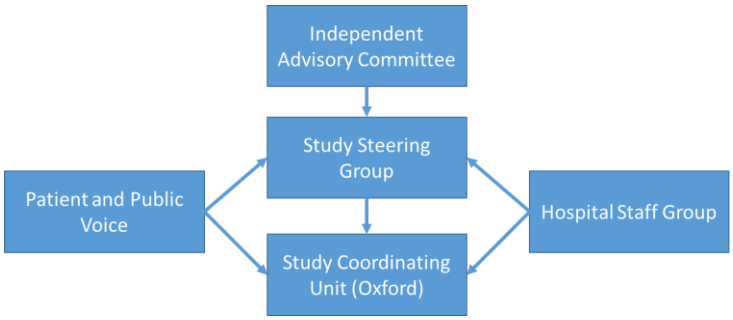

Fig. 1: Study governance structure.

18. Approval by ethics committees

Most of the work included in the present proposal involves analysis of existing studies, and application of health economic analyses to their output. The study also includes workshops and surveys of women who would be the target population for future studies. Ethics approval to conduct workshops and surveys with women to discuss their attitudes to screening will be obtained prior to the start date.

19. Patient and Public Involvement

We have formed a strong PPV group, a core element of this work. This group have co-authored this application. They have already provided invaluable support for the different work packages, including prioritising what evidence needs to be found and how to deal with lack of evidence; on current care pathways; on the role of patient preferences in consensus building; and what metrics in economic analysis could be sensible when thinking about screening for a condition earlier in pregnancy. The group will continue in the study governance structure (see section **18. Project management**). The chair of the group will sit on the SSG, as will Jane Fisher, the CEO of Antenatal results and Choices (ARC) - a charity that provides non-directive information and support to parents before, during and after antenatal screening; when they are told their baby has an anomaly; when they are making difficult decisions about continuing with or ending a pregnancy, and when they are coping with complex and painful issues after making a decision, including bereavement. The other members of the group are:

Jon Arnold, from the charity Tiny Tickers – whose mission is to improve the early detection and care of babies with serious heart conditions, as this can save lives, improve post-surgery survival rates and lead to a better long-term quality of life.

Gill Yaz, who directs Health and Policy issues at SHINE (Spina Bifida - Hydrocephalus - Information - Networking – Equality), a charity that aims for a society that meets the needs, values the contribution and celebrates the lives of people living with spina bifida and hydrocephalus. The group have an interest in antenatal screening, including for other neural tube defects (e.g. anenecepahly) that may be detected in the first trimester. The charity has recently launched a large survey of parents to help improve antenatal services.

Elizabeth Duff, of the National Childbirth Trust, the UK's largest parent's charity, that amongst other issues, offers information and support in pregnancy, birth and early parenthood; campaigns to improve maternity care and ensure better services and facilities for new parents and aims to give every parent the chance to make informed choices.

The PPV group will be one of the channels that allows us to engage women and the public. However, while we are clearly aware of the constituency of parents who have had anomalies detected during pregnancy, we are also very aware that there are many other constituencies, and that different groups will have different perspectives and priorities. We regard it as essential that all perspectives are included in our assessment of the views of women and the public, and consultation with other groups may also occur.

20. Expertise and justification of support required

20.1 Particular expertise and contribution by each member of the team

Aris Papageorghiou will provide overall leadership and day-to-day management of the project. He is a clinical academic and practising Fetal Medicine specialist. His research is focused on the development and quality assessment of tools for screening pregnant women for adverse outcomes of pregnancy; and large scale evaluation of such tools. As part of this work he has conducted a number of systematic reviews and meta-analyses of observational data; has conducted large scale, multicentre, prospective observational and screening studies; has participated in large randomised trials related to fetal medicine; and conducted Delphi concensus procedures. He has published extensively in this field including in the Lancet, BMJ, JAMA and Pediatrics. Of particular relevance he has published systematic reviews of first trimester ultrasound screening for anomalies in singletons (1) and twins (68) as well as first trimester ultrasound for fetal measurement (69). He will directly supervise the research associate.

Health economics team

Oliver Rivero-Arias directs a team of health economists at the National Perinatal Epidemiology Unit (NPEU). He is a senior researcher in health economics at the NPEU and has extensive experience of leading applied health economic evaluations in the field of maternal and child health. He will oversee and manage the economic analytic aspects of the current proposal.

Helen Campbell is a senior health economist at the NPEU and has over 20 years' experience in conducting model and trial-based health economic evaluations. She will undertake the day-to-day analysis of the health economics part of the project.

Ed Wilson is a health economist at the University of Cambridge with over 15 years' experience. He has particular methodological expertise in efficient research design, specifically in VoI analysis. Of relevance here, he has published a practical guide to VoI (70); a review of methods for quality assessment in decision analytic modelling (71), and is overseeing the related health economic analysis of the NIHR Health Technology Assessment Reference: 15/105/01 (Late pregnancy ultrasound). Ed will lend his expertise in VoI analysis to the project and supervise DW in the running and re-running of this under different trial designs.

David Wastlund is a research assistant in health economics at the Cambridge Centre for Health Services Research (CCHSR) with experience in developing decision analytic models for evaluating the cost-effectiveness of ultrasound screening in late pregnancy. Under the guidance of ORA and EW he will design and re-run the VoI analysis for plausible prospective studies.

Patient and Public Voice

Jane Fisher, the CEO of Antenatal results and Choices (ARC) - a charity that provides non-directive information and support to parents before, during and after antenatal screening; when they are told their baby has an anomaly; when they are making difficult decisions about continuing with or ending a pregnancy, and when they are coping with complex and painful issues after making a decision, including bereavement. Jane will advise on parental perceptions.

Jon Arnold, from the charity Tiny Tickers – whose mission is to improve the early detection and care of babies with serious heart conditions, as this can save lives, improve post-surgery survival rates and lead to a better long-term quality of life.

Gill Yaz, who directs Health and Policy issues at SHINE (Spina Bifida - Hydrocephalus - Information - Networking – Equality), a charity that aims for a society that meets the needs, values the contribution and celebrates the lives of people living with spina bifida and hydrocephalus. The group have an interest in antenatal screening, including of other neural tube defects (e.g. anenecepahly) which may be detected in the first trimester. The charity has recently launched a large survey of parents to help improve antenatal services.

Elizabeth Duff, of the National Childbirth Trust, the UK's largest parent's charity, that amongst other issues, offers information and support in pregnancy, birth and early parenthood; campaigns to improve maternity care and ensure better services and facilities for new parents; and aims to give every parent the chance to make informed choices.

Clinical expertise in fetal scanning / screening / observational studies:

Trish Chudleigh is the Lead Sonographer at Rosie Hospital, Cambridge; Education Consultant to the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG); and represents the British Medical Ultrasound Society (BMUS). She is the author of several influential books and papers on the practice of ultrasound. She will primarily advise on screening pathways from the point of view of sonographers; and will also be an important link to disseminate findings in the sonographer community through contributions to the BMUS journal and meeting.

Gordon Smith researches improved screening methods for placentally-related complications of pregnancy, funded by the NIHR Cambridge Biomedical Research Centre (theme lead for Women's Health and Paediatrics) and the MRC. He has published extensively on the clinical epidemiology of adverse pregnancy outcome. He is PI on an HTA funded evidence synthesis and value of information analysis for screening using universal late pregnancy ultrasound. He will provide input into the evidence synthesis and design of future observational studies or trials, with a particular focus on sample size considerations.

Hilary Goodman has extensive expertise in screening and antenatal services. She is currently the operational manager for antenatal services and screening at the Hampshire Hospitals Foundation Trust, and a member of the UK National Screening Committee. She is also a peer reviewer for the Antenatal and Newborn Screening Programmes. She will provide insights into the midwifery environment at and input into feasibility of screening pathways.

Pranav Pandya, is a Consultant in Fetal Medicine at University College London Hospitals and Chair of the Fetal Anomaly Screening Programme Advisory Group at the NSC. He has published extensively on first trimester ultrasound and screening for fetal aneuploidy and anomalies. He is the chair the Fetal Anomaly Screening Programme (FASP) Advisory Board which will be responsible for establishing a guideline for routine first trimester anomaly ultrasound in England. This is important as FASP would also take the lead on training sonographers, implementation and audit.

Ms Heather Longworth is antenatal screening midwife at Liverpool Women's Hospital NHS Trust; she oversees all first trimester screening and is closely linked to the ultrasound scanning department. Liverpool is the largest single site maternity hospital in the UK and Heather will provide advice on potential barriers to implementation of any screening programme in the clinical setting.

Kypros Nicolaides is a Professor of Fetal Medicine at King's College Hospital, London and director of the Fetal Medicine Foundation. He is one of the pioneers of fetal medicine and a major part of his work over the years is regarding the 11-13+6 weeks ultrasound scan assessment, including measurement of nuchal translucency. He has contributed to over 1500 journal articles and more than thirty books and monographs, including the largest screening study to date of first trimester ultrasound for fetal anomalies.

Basky Thilagnathan, St George's London, researches and has published extensively on fetal anomaly screening, detection and management. He is the Director of the Southwest Thames regional Fetal Medicine Service at St Georges Hospital NHS Foundation Trust and the Editor-in-Chief of Ultrasound in Obstetrics and Gynecology - the leading journal covering the topic of fetal anomaly management. He is the Royal College of Obstetrics and Gynaecologists (RCOG) representative on the Fetal, Maternal and Child Health subcommittee of the National Screening Committee (NSC). He will provide input into the evidence synthesis and design of future observational studies or trials, with a special translational focus on study design and implementing relevant findings.

Trial design:

Ed Juszczak is the Director of the NPEU Clinical Trials Unit. He has extensive experience of all aspects of multi-centre perinatal RCTs. He will advise on the feasibility, design, conduct and statistical aspects of the potential trial.

Louise Linsell is a senior statistician at the NPEU Clinical Trials Unit and has extensive experience in the design and analysis of perinatal RCTs. She will advise on all statistical aspects of the potential trial.

Zarko Alfirevic is Director of Fetal Medicine Unit at Liverpool Women's Hospital and Co-ordinating Editor of Cochrane Pregnancy and Childbirth Group. A highly experienced as a PI in major, multi-centre RCTs and evidence synthesis, he is also the lead author of the ISUOG Practice Guidelines on the performance of the first-trimester fetal ultrasound scan. He will primarily provide input into the evidence synthesis and design of future randomised controlled trials.

Jim Thornton is a highly experienced as a PI in major, multi-centre RCTs as well as experience in evidence synthesis. He will primarily provide input into the evidence synthesis and design of future randomised controlled trials.

Qualitative Research:

Lisa Hinton is a senior qualitative researcher who leads applied research for the Health Experiences Research Group (HERG) in the Nuffield Department of Primary Care Health Sciences (NDPCHS) at Oxford. HERG is a well-established academic group of social scientists that use qualitative research to understand patient health experiences. She has particular expertise in maternal and neonatal health and leads the Patient Experiences Sub-theme in the Partnerships for Health, Wealth and Innovation cross-cutting theme of the Oxford NIHR

Biomedical Research Centre (BRC). She will advise on considerations regarding parental experiences of, and views on, fetal ultrasound, and bring her PPI expertise to the PPV group.

20.2 Supervision arrangements for junior staff involved:

We have requested funding for a research associate (0.8FTE). The remaining 0.2 FTE will be clinical work; in our experience the offer of continuing with 0.2FTE clinical work makes these posts more attractive and opens the field of applicants. The Research associate will undertake the day to day management of the study and be supervised directly by the lead applicant.

20.3 Justification of funding

We have taken the Board's views into consideration and have looked carefully at all costs and reduced these wherever feasible. The group have critically reviewed and discussed the outline application in relation to the commissioning brief; and consulted closely with the PPV group. As a result we have removed the previous WP4. It was felt that this qualitative research project constituted original research and was beyond the commissioning brief. Assessment of the acceptability of the early anomaly scan will now be undertaken through consultation rather than primary qualitative research. It should be noted that separate funding wil be sought for the original WP 4.

The consensus procedure has been changed in scope to a wide-ranging scoping and consultation exercise rather than a formal Delphi process. This decision was taken because it was felt that the large and diverse Study & Advisory Group would ensure appropriate representation of all relevant groups. This will be supplemented with wide-ranging consultation amongst professional groups and parents using more cost effective means (e.g. survey monkey). The advantages of this approach are that the results will be available earlier; and it will also cost much less. However, we will adhere to the same stringent criteria and HTA recommendations on consensus development methodology.

The main bulk of the project is for a research associate. We have reduced this to 0.8FTE with the remaining 0.2 FTE as clinical work; this makes clinical posts more attractive and also allows the applicant to be in touch with the clinical team, which is beneficial for the project. It was felt inappropriate to reduce the duration or payscale of the post as we anticipate multiple systematic reviews of observational studies.

The project involves extensive health economic analysis, both the value of information analysis referent to the proposed trial, and the health economic analysis of the proposed screening. The board specifically questioned why four health economists are involved; it should be noted that HC will be on this project for 50% of her time and EW and ORA contribute a relatively small amount for supervision. DW will be involved in the VOI analysis and as he is now funded from other sources for year one, his funding has been reviewed and reduced to encompass the second year of the project only. Completing both a health economic analysis of screening and a major value of information analysis is ambitious; we believe it would be unduly optimistic to achieve this in less than 2 years.

A large proportion of the budget is related to the number of hours the applicants have committed to the project. In light of the committee's comments that costs should be reviewed to ensure value for money, we have reduced the hours of the co-applicants; it is a credit to their commitment that they have agreed to this while at the same time ensuring participation for the successful delivery of the project.

Additional costs are related to meetings and surveys. These will include quarterly face to face meetings of the applicants, and conducting consensus meetings with clinicians and the public. These are essential as detailed discussions of the results of systematic reviews, economic evaluation and VoI analysis need to occur; this resource is therefore required to develop the screening and management protocols. In addition meetings of the applicants are essential for the effective running of the project, and full utilisation of the broad range of skills among the applicants to prosecute the project.

There are no major equipment costs attached to the project, with the only additional costs for software licence and a laptop computer.

There are no anticipated NHS Support Costs or Excess Treatment Costs associated with this proposal.

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22. Department of Health and Social Care disclaimer

The views expressed are those of the authors(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

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