The DESiGN Trial

DEtection of Small for GestatioNal age fetus (SGA) – a cluster randomised controlled trial to evaluate the effect of the Growth assessment protocol (GAP) programme

Version	6.0
Date	15/11/2015
Sponsor	University College London (UCL)
Comprehensive Clinical Trials Unit Trial Adoption Group #	CTU/2015/173
Trial registration	[ISRCTN67698474]
CTA #	[insert CTA number]
NRES #	[15/LO/1632]

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1 Administrative information

This document was constructed using the Comprehensive Clinical Trials Unit (CCTU) at UCL Protocol template Version 4. It describes the DESiGN trial, sponsored by UCL and co-ordinated by CCTU.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the trial. Sites entering participants for the first time should confirm they have the correct version through a member of the trial team at CCTU.

CCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on an adaptation of the Medical Research Council CTU protocol template (2012) and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials (1). The SPIRIT Statement Explanation and Elaboration document (2) can be referred to, or a member of CCTU Protocol Review Committee can be contacted for further detail about specific items.

1.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

Participating sites will inform CCTU as soon as they are aware of a possible serious breach of the protocol, so that CCTU can fulfil its requirement to report the breach if necessary to the Research Ethics Committee.

1.2 Sponsor

UCL is the trial sponsor and has delegated responsibility for the overall management of the DESiGN trial to CCTU. Queries relating to UCL sponsorship of this trial should be addressed to the CCTU Director or via the trial team.

1.3 Structured trial summary

Primary Registry and Trial Identifying Number	ISRCTN67698474
Date of Registration in Primary Registry	02/11/2016
Secondary Identifying Numbers	Not applicable
Source of Monetary or Material Support	Tommy's Charity SANDS Guy's and St Thomas' Charity
Sponsor	University College London with sponsor responsibilities delegated to CCTU.
Contact for Public Queries	ctu.enquiries@ucl.ac.uk
Contact for Scientific Queries	Dr Dharmintra Pasupathy Senior Lecturer / Consultant in Maternal & Fetal Medicine and Perinatal Epidemiology Division of Women's Health Women's Health Academic Centre KHP 10th Floor North Wing St. Thomas' Hospital Westminster Bridge Road London SE1 7EH Tel no: 020 7188 4137/4138 Email: Dharmintra.Pasupathy@kcl.ac.uk
Public Title	Improving detection of small infants during pregnancy.
Scientific Title	**The DESiGN Trial -** Detection of small for gestational age fetus (SGA) – a cluster randomised controlled trial to evaluate the effect of the Growth Assessment Protocol (GAP) programme
Countries of Recruitment	UK
Health Condition(s) or Problem(s) Studied	Small for gestational age (SGA) fetus and infants
Intervention(s)	GAP programme. This includes comprehensive staff training, evidence-based protocols, routine monitoring of SGA and detection rates, regular audits of missed cases to help identify training needs and system failures in fetal growth surveillance, and ongoing communication and support between the Perinatal Institute and Trusts.
Key Inclusion and Exclusion Criteria	Inclusion and exclusion criteria into the study listed below is based on characteristics of the maternity unit (cluster). There are no inclusion or exclusion criteria based on women within each maternity unit (cluster). Data from all pregnant women within each maternity unit (cluster) will be collected. Inclusion criteria: Maternity units which are willing to implement the GAP programme. Exclusion criteria: Maternity units which have already implemented GAP or will not be introducing GAP.
Study Type	Cluster randomised controlled trial
Date of First	3rd of November 2016

Randomisation	
Target Sample Size	12 Maternity Units (Clusters). Power calculation based on average of 5000 birth per year per maternity unit (cluster) with a SGA prevalence of 10%.
Primary Outcome	Ultrasound detection of infants that are SGA (birthweight <10th centile) by both customised and population standards that were detected antenatally after 24 weeks*. * The antenatal charts used for ultrasound detection (numerator) will depend on the allocation arm of the trial. The denominator for the estimation of detection in each arm of the trial will be the same population of SGA infants (SGA by both customised and population).
Key Secondary Outcomes	A. Ultrasound detection of SGA at birth by customised centiles defined as the proportion of SGA infants (birthweight <10th customised centile) that were detected antenatally by ultrasound scan after 24 weeks. We will determine the additional diagnostic test performance (specificity, false positive and false negative). B. Ultrasound detection of SGA at birth by population centiles (UK90 population centiles) defined as proportion of SGA infants (birthweight <10th population centile) that were detected antenatally by ultrasound scan after 24 weeks. We will determine the additional diagnostic test performance (specificity, false positive and false negative). C. Effect on short term clinical outcomes 1. Neonatal – *general parameters* - gestational age at birth, birthweight, head circumference; *parameters related to immediate condition at birth* - 5-min Apgar score <7, delivery with metabolic acidosis (arterial cord ph<7.1), respiratory support in delivery room; *parameters related to NICU admission* – length of stay, level of care, major neonatal morbidity – one or more of the following - intraventricular haemorrhage, supplementary oxygen requirements > 28 days, necrotizing enterocolitis, sepsis, retinopathy of prematurity; *parameters related to transitional care* – length of stay, neonatal morbidity – one or more of the following - hypothermia, hypoglycaemia, nasogastric tube feeding; *perinatal loss* – stillbirth (antepartum and intrapartum), neonatal death (early and late), death before discharge (after 28 days of birth). In all perinatal losses we will also record cause of death. 2. Maternal - induction of labour; mode of delivery including caesarean section rates; postpartum haemorrhage (>1000ml); severe perineal trauma (3rd / 4th degree tear), length of stay in hospital; breast feeding at discharge; pre-eclampsia; gestational diabetes mellitus. D. Health economics - number of ultrasound scans after 24 weeks; antenatal clinic / antenatal day unit activity; rates of induction of labour; rates of caesarean sections; length of maternal and neonatal stay; admissions and average length of stay in NICU / SCBU

	E. Process evaluation of implementation: proportion of staff trained, staff assessed and women assessed with GAP programme; adherence to SGA risk stratification and management protocols and missed case analysis. Evaluation of acceptability and feasibility of intervention to staff and women, contextual barriers and facilitators and organisational impact. F. Other methods of assessments of antenatal detection of SGA: 1. Ultrasound detection of SGA using different threshold (e.g. 5^{th} centile). 2. Clinical detection of SGA at birth (by customised centiles): defined as the proportion of SGA infants (birthweight $<10^{th}$ customised centile) that were clinically detected antenatally (by ultrasound scan after 24 weeks and clinically defined/managed as SGA) in each arm. 3. Growth trajectories (fetal biometry and EFW) and Doppler parameters in the detection of SGA. 4. GROW ultrasound charts (which is single component of GAP) against standard population charts on classification of fetal growth (small for gestational age, appropriate for gestational age, large for gestational age).

1.4 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF for current lists.

1.4.1 Protocol contributors

Name	Affiliation	Role
Dr Dharmintra Pasupathy	Division of Women's Health, KCL	Design of trial Protocol development Review of protocol
Dr Asma Khalil	Department of Obstetrics, St George's Hospital	Design of trial Protocol development Review of protocol
Professor Jane Sandall	Division of Women's Health, KCL	Design of process evaluation Design of trial Review of protocol
Dr Matias Costa Vieira	Division of Women's Health, KCL	Design of trial Protocol development Review of protocol
Dr Andrew Copas	UCL CCTU	Statistical analysis plan & sample size calculation Protocol development Review of protocol
Mr Paul Seed	Division of Women's Health, KCL	Sample size calculation
Mrs Caroline Doré	UCL CCTU	Senior statistical oversight Advice on design of trial Review of protocol
Ms Susan Tebbs	UCL CCTU	Advice on design of trial Protocol development Review of protocol

1.4.2 Co-investigators

Name	Affiliation	Role
Professor Peter Brockelhurst	UCL	Review of protocol Director of UCL CTU
Professor Mark Johnson	Imperial	Review of protocol
Professor Debbie Lawlor	University of Bristol	Epidemiological advice on study design
Professor Lesley McCowan	University of Auckland	Advice on design of trial & GAP
Professor Neil Marlow	UCL	Advice on neonatal outcome measures
Professor Donald Peebles	UCL	Link with Strategic Clinical Network for participation of sites
Professor Andrew Shennan	KCL	Review of protocol
Professor Basky Thilaganathan	St George's	Topic expert on fetal growth
Dr Annette Briley	KCL	Study implemention

Dr Kirstie Coxon	KCL	Design of process evaluation
Dr Andy Healey	KCL	Health economics
Dr Christoph Lees	Imperial	Topic expert on fetal growth
Dr Louise Page	West Middlesex NHS trust	Review of protocol
Dr Matias Costa Vieira	KCL	Design of trial Protocol development Review of protocol
Mrs Alessandro Alagna	Tommy's Charity	Representation of patient group

1.4.3 Site investigators

Name	Affiliation	Role
Simona Cicero	Homerton	Conduct of trial in local participating site
Donald Peebles	UCH	Conduct of trial in local participating site
Claire Rozette	GSTT	Conduct of trial in local participating site
Edwin Chandraharan	St George's	Conduct of trial in local participating site
Elisabeth Peregrine	Kingston	Conduct of trial in local participating site
Naguib Fayez	Croydon	Conduct of trial in local participating site
Mandish Dhanjal	Imperial	Conduct of trial in local participating site
Paula Galea	Hillingdon	Conduct of trial in local participating site
Hiran Samarage	Northwick Park	Conduct of trial in local participating site
Louise Page	West Middlesex	Conduct of trial in local participating site
Renata Hutt	Royal Surrey	Conduct of trial in local participating site
Deepa Janga	North Middlesex	Conduct of trial in local participating site
Janet Cresswell	Chesterfield	Conduct of trial in local participating site
Nusrat Fazal	Great Western Hospitals	Conduct of trial in local participating site

1.4.4 Role of trial sponsor and funders

Name	Affiliation	Role
UCL	UCL	Sponsor
Tommy's Charity		Funder – no involvement in development and reporting of the trial.
Stillbirth & neonatal death charity (SANDS)		Funder – no involvement in development and reporting of the trial.
Guy's and St. Thomas' Charity (GST)		Funder – no involvement in development and reporting of the trial.

1.4.5 Trial Team

Name	Affiliation	Role and responsibilities
Dr Dharmintra Pasupathy	Division of Women's Health, KCL	Chief investigator
TBC	UCL CCTU	Clinical project manager
TBC	UCL CCTU	Trial manager
TBC	KCL	Data Collection Midwives / Data manager
TBC	UCL CCTU	Data programmer
Dr Annette Briley	Division of Women's	Conduct of trial

	Health, KCL	
Dr Matias Costa Vieira	Division of Women's Health, KCL	Conduct of trial
Ms Susan Tebbs	UCL CCTU	Deputy Director CCTU. Link with CCTU

1.4.6 Trial Management Group

Name	Affiliation	Role and responsibilities
Dr Dharmintra Pasupathy	Division of Women's Health, KCL	Conduct of trial
Dr Asma Khalil	Department of Obstetrics, St George's Hospital	Conduct of trial Clinical link for South West London
Professor Jane Sandall	Division of Women's Health, KCL	Implementation evaluation
Professor Donald Peebles	UCL	Link with London Maternity Strategic Clinical Network
Dr Annette Briley	Division of Women's Health, KCL	Conduct of trial
Dr Matias Costa Vieira	Division of Women's Health, KCL	Conduct of trial
Dr Andrew Copas	UCL CCTU	Statistical analysis
Dr Andrew Healey	KCL	Health economics
Ms Susan Tebbs	UCL CCTU	Deputy Director CCTU. Link with CCTU

1.4.7 Trial Steering Committee / Data Monitoring Committee

Name	Affiliation	Role and responsibilities
Proposed members include:		
Professor Zarko Alfirevic	University of Liverpool	Chair
Professor Marian Knight	National Perinatal Epidemiology Unit (NPEU)	Vice-Chair
Dr Ed Juszczak	NPEU	Statistician
CCTU Member	TBC	TBC
TBC	TBC	Clinician
TBC	TBC	Clinician
SANDS / TOMMY's PPI involvement	TBC	PPI Involvement

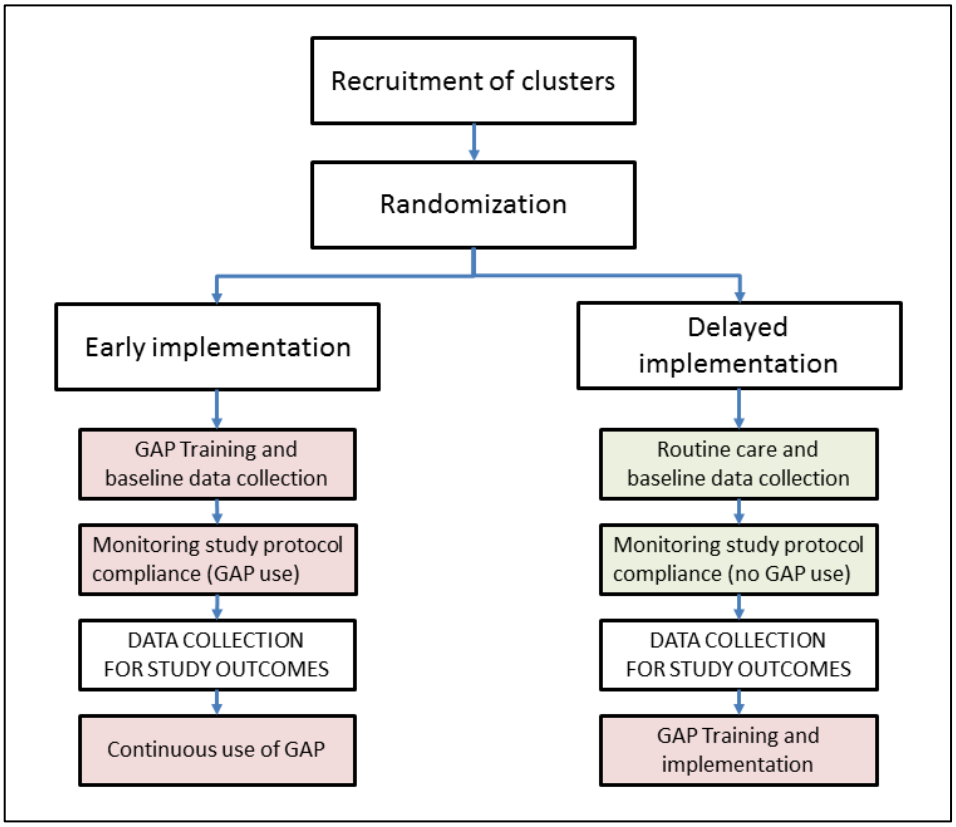
1.4.7 Other Trial Oversight Groups

Name	Affiliation	Role and responsibilities

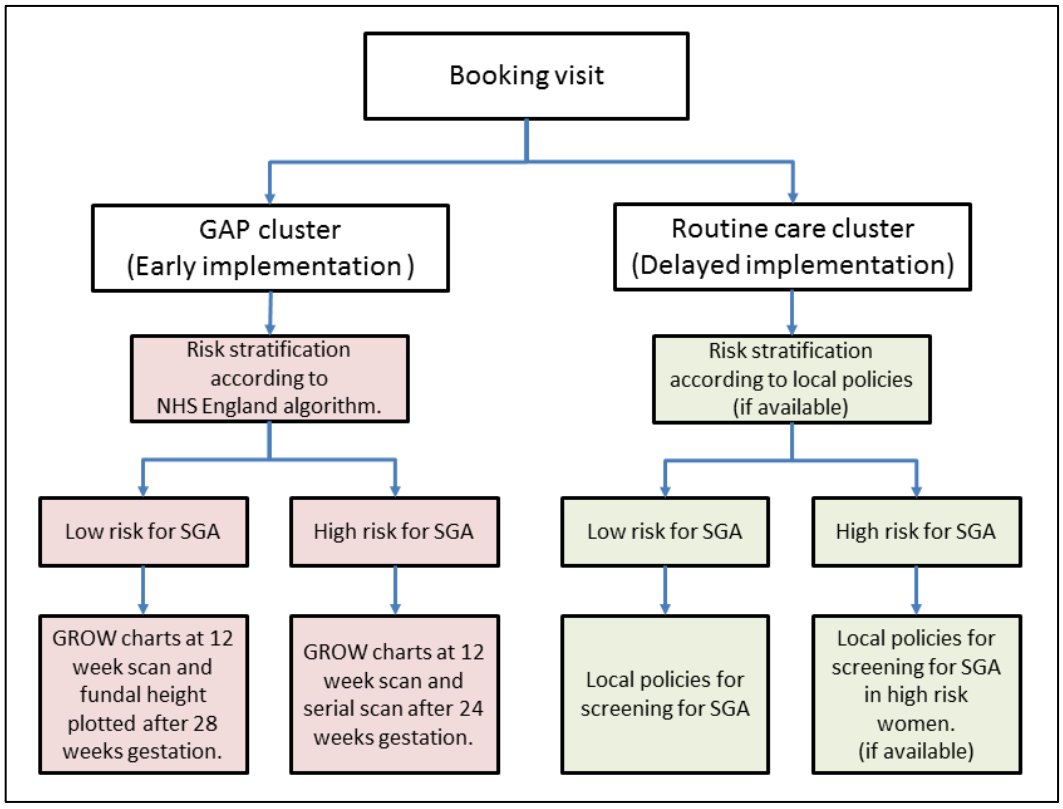
UCL CCTU Quality Management Group (QMG)	UCL CCTU	Oversight of general governance and compliance
UCL CCTU Protocol Review Committee	UCL CCTU	Review of the protocol
Stillbirth Clinical Study Group	RCOG	Review of the protocol

2 Trial Diagram

2.1 Diagram of cluster (hospital) participation



2.2 Diagram of individual management within participating clusters (hospitals)



3 Abbreviations

AE	Adverse Event
AR	Adverse Reaction
BMI	Body Mass Index
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CCTU	Comprehensive Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EU	European Union
FDA	(US) Food and Drug Administration
FH	Fundal height
FWA	Federal Wide Assurance
GAP	Growth Assessment Protocol
GCP	Good Clinical Practice
GROW	Gestation Related Optimal Weight
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention to Treat
KCL	King's College London
LGA	Large for Gestational Age
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health System
NICU	Neonatal Intensive Care Unit
NPEU	National Perinatal Epidemiology
	Unit
ONS	Office of National Statistics
PI	Principal Investigator
PIN	Participant Information Number
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SFH	Symphysis Fundal height
SGA	Small for Gestational Age
SCBU	Special Care Baby Unit
SPC	Summary of Product Characteristics
SSA	Site Specific Approval
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
ToR	Terms of Reference
TSC	Trial Steering Committee
UCL	University College London

4 Glossary

Term *(and abbreviation if applicable)*	***Definition***
Breastfeeding at discharge	Feeding method stated on discharge from hospital.
Gestational age at delivery	Gestational age in weeks and days. Ideally calculated from 1st trimester scan as per NICE guidelines (CG62 1.2.6).
Gestational diabetes mellitus	Ideally by an oral glucose tolerance test (as per NICE CG63/WHO) but otherwise by local hospital guidelines, as recorded in the hospital notes or IT records.
Large for gestational age by customised centiles	Birthweight above 90th centile by customised centiles.
Large for gestational age by population centiles	Birthweight above 90th centile by population centiles (UK90 population centiles).
Length of stay (maternal)	Length of time in days spent as an inpatient in hospital either from antenatal admission or from admission in labour or induction until discharge following birth.
Length of stay (neonatal)	Length of time in days spent as an inpatient in hospital following birth (includes time in NICU as well as postnatal or neonatal / paediatric ward). It does not count readmission.
Length of stay in Neonatal intensive care unit (NICU) admission.	Length of stay in days on NICU.
Length of stay in Special care baby unit (SCBU) admission.	Length of stay in days on SCBU
Major neonatal morbidity	One or more of the following - intraventricular haemorrhage, supplementary oxygen requirements> 28 days, necrotizing enterocolitis, sepsis, retinopathy of prematurity
Need for transitional care	Any duration of transitional care.
Neonatal intensive care unit admission.	Admission to NICU
Neonatal morbidity	One or more of the following - hypothermia, hypoglycaemia, nasogastric tube feeding

Term *(and abbreviation if applicable)*	***Definition***
Number of antenatal visits	Number of antenatal visits after 24 weeks per pregnancy.
Postpartum haemorrhage	Percentage of women giving birth who had an estimated blood loss of greater than 1000ml.
Pre-eclampsia	Clinical diagnosis of pre-eclampsia as recorded in the hospital notes or IT records.
Small for gestational age by customised centiles	Birthweight less that the 10th centile by customised centiles.
Small for gestational age by population centiles	Birthweight less than the 10th centile by population centiles (UK90 population centiles).
Severe perineal trauma	Defined as any third or fourth degree tear (affecting the anal sphincter muscle(s) or rectal mucosa) (RCOG GTG29).
Special care baby unit admission	Admission to SCBU
Stillbirth	Number of babies delivered without signs of life, ≥24+0 weeks of gestation. Expressed per 1000 births (live births and stillbirths).

5 Introduction

5.1 Background and Rationale

The rate of stillbirth in the UK has changed little over the past 20 years and remains amongst the highest in developed countries (3, 4). The impact of a stillbirth is extensive, not only for the family but has consequences for the society. Reducing stillbirth is currently a national priority. Until recently two thirds of stillbirths were considered unexplained and, therefore unavoidable. Using a new classification system it has been demonstrated that 43% of babies who died in utero were small for gestational age (SGA) and 9% had placental insufficiency (5). A subsequent population based study has shown that antenatal detection of SGA can halve the stillbirth risk (6).This suggests that improvements in the detection of SGA infants could have the potential to significantly reduce the incidence of stillbirths.

At present the antenatal detection of SGA is poor and antenatal identification is achieved in only about 1 in 4 cases (6-8). Improved antenatal detection of SGA is recognised to improve pregnancy outcome through appropriate antenatal surveillance and timely delivery (6, 9). SGA was traditionally defined as birth weight below the 10th centile for gestational age and sex according to population references (4, 10). SGA by population centiles is associated with many adverse neonatal outcomes including stillbirth and perinatal death (11, 12). However, SGA by population birth weight centiles does not account for physiological maternal characteristics and includes the effects of pathological pregnancies, such as pre-eclampsia, that may affect fetal growth. Thus some infants, currently defined as SGA, may be appropriately grown for maternal constitution, whereas others which are growth restricted will not be defined as SGA. The concept of customised centiles attempts to address these issues and is based on three principles: individualised (adjustment for physiological factors that affect birth weight), optimised growth potential (excluding pathological factors affecting the weight standard such as smoking and diabetes) and use of fetal standards. The use of customised centiles, which adjust for maternal height, weight, ethnicity, parity, gestation at delivery, and fetal sex, identifies additional SGA fetuses which would not have been identified by conventional definitions (13). These infants who are SGA only by customised standards are at increased risk of adverse outcomes, including stillbirth. Crucially, fetuses that are considered SGA only by population centiles seem to have similar outcomes as appropriately grown fetuses (13).

Despite the evidence described above, customised centiles have been criticised because some factors might not have a physiological effect (14-16). This is especially true for maternal weight and ethnicity. Obesity is characterised by a metabolic disturbance that affects fetal growth and is associated with increased perinatal morbidity and stillbirth (17). However, Gardosi *et al.* have demonstrated that variation of maternal weight was not associated with increased risk of perinatal mortality, in women with a body mass index (BMI) within the normal range (20-25kg/m^2). In the cohort with BMI >25kg/m^2, there was no correlation between SGA rates by population centiles and rates of perinatal mortality. However rates of SGA by customised centiles and perinatal mortality were correlated (18). This study does not address the cause of perinatal mortality, which may not relate to SGA. The cause specific mortality related to SGA may differ by BMI category. The influence of ethnicity is more complex as it is recognised that there is an association between ethnicity and socio-economic deprivation (19, 20). Socioeconomic deprivation also has an association with antepartum stillbirth risk (21, 22). Therefore any adjustment for maternal ethnicity has the potential to adjust for the pathological effects of socioeconomic deprivation. In a recent publication from a

multicentre international study, an international fetal standard was developed using 8 cohorts of pregnant women in optimal conditions, who were at low risk of fetal growth anomalies (23). The authors describe a similar ultrasound growth potential and birthweight distribution across all participating countries which suggests that no physiological association exists between ethnicity and fetal weight, following exclusion of other potential confounding variables. Although these Intergrowth data demonstrate that infants born in India to well nourished women, had a mean birthweight of 600g lower than infants born in the UK, using skeletal size as markers of growth there was considered to be sufficient similarity in the distribution of the data to construct an international pooled growth standard used for screening of growth anomalies (23, 24). Kierans *et al.* have used the Canadian stillbirth registry and reported that using population standards there was a higher rate of SGA in women of Chinese and South Asian ethnicity. However the perinatal mortality rate in this group was the lowest compared to other groups. Using customised standards, the rate of SGA was lower in Chinese and South Asian ethinicity and more importantly concordant with the prevalence of perinatal mortality in this population (25). According to current evidence, adjustment for ethnicity seems reasonable as it improves the detection of SGA infants at risk of morbidity and mortality although a pathological effect may exist and this may differ by socioeconomic groups between different populations studied.

At present in most UK obstetric units, the suspicion of fetal growth restriction is firstly assessed by palpation of the maternal abdomen. Symphysis fundal height (SFH) measurement is a screening tool for SGA, however, the accuracy is limited (26, 27). A non-randomised controlled trial of standardised fundal height (FH) measurement and estimated fetal weight plotted on customised charts demonstrated an increase in antenatal detection of small babies (48% vs. 29%, odds ratio 2.2; 95%CI 1.1-4.5) (28). Implementation of these charts was also tested in Australia where there was also a doubling in the detection rate of SGA compared with historical controls (29).

The Growth Assessment Protocol (GAP) is a training programme developed by the Perinatal Institute that consists of use of Gestation Related Optimal Weight (GROW) charts linked to risk assessment, management protocols and audit tools. GROW utilises a systematic method of measurement, achieved through a standardised training and accreditation programme, with the use of FH charts, developed in accordance with the principles of customisation. Estimated fetal weights from ultrasound assessment are also plotted on these customised fetal growth charts. The second component of GAP is the risk assessment and management protocols linked to key points from the RCOG Green-top Guideline on Investigation and Management of the Small-for-Gestational-Age fetus (30). It also includes a missed case audit tool to assess reasons for failure of antenatal recognition of SGA. The development of GAP as a comprehensive programme has been more recent with previous implementations being mainly focused on GROW with aspects of case reviews, audit and management guidance.

The use of the GAP / GROW programme has expanded since its development and is now implemented in 105 (64%) of UK Trusts (31). Gardosi *et al.,* have recently reported the impact of the programme in UK comparing regions with high uptake to regions with low uptake between 2007 to 2012 using data from Office for National Statistics (ONS) records (32). The results have demonstrated that high uptake of the programme was associated with a reduction in stillbirth rates. Overall, there was an impressive 22% reduction in stillbirth rates in the high uptake regions during the period analysed, which reflects the period before and after implementation of GAP / GROW. This

observational study fulfilled the Bradford Hill (33) criteria for causality. However, it is recognised that the highest level of evidence is obtained from randomised controlled trials, which is lacking in this area as highlighted in a Cochrane review (34). Therefore a randomised controlled trial to accurately assess the GAP programme is imperative and timely.

Furthermore, the effect of the GAP on the management of pregnancies and other maternal and neonatal outcomes, such as caesarean section rates, induction of labour, gestational age at delivery, neonatal intensive care unit admission, prenatal detection of large for gestational age (LGA) infants, neonatal morbidity and length of stay in hospital is less well reported. Introduction of the GAP programme will also have an impact on health economics and clinical service provision, partly from the outcomes discussed above (such as induction of labour, caesarean section, and length of stay) but also related to utilisation of scanning, which requires evaluation. This independent evaluation will inform the planning of clinical service provision and inform national policy makers on financial implications for maternity care. This must also be balanced against the importance of some key neonatal outcomes (stillbirth, early neonatal death, neonatal morbidity due to brain injuries).

London has a prevalence of stillbirth above the national mean (2013 data: London 5.3/1000 (35) UK 4.8/1000 (36)) and the use of GAP in clinical practice is very low at present (approx. 5%). The London Maternity Network has recommended the use of GAP as a strategy for reduction in stillbirth rates and Trusts are increasingly interested in adopting this package. Given the incomplete usage in London and the current evidence base from observational studies this provides a unique opportunity to undertake a Cluster Randomised Controlled Trial (RCT) to assess the impact of the GAP programme. A study powered to investigate stillbirth as a primary outcome will require a large sample size (37, 38). To study a similar outcome and achieve similar power we will require 346 hospitals (clusters) per arm. It is recognised that improved detection of SGA is associated with a reduction in the risk of stillbirth (9). Therefore we propose a cluster RCT to evaluate the GAP programme as a strategy for improving the antenatal detection of SGA, including implementation evaluation and health economic assessment.

5.1.1 Explanation for choice of comparators

A cluster randomised controlled trial comparing the effect of the introduction of GAP to current clinical practice on pregnancy outcomes and service provision.

5.2 Objectives

- To determine whether implementation of the GAP programme will result in an improved ultrasound and clinical detection of SGA.
- To investigate the effect of the intervention on short-term maternal and neonatal outcomes
- To estimate the impact of GAP on clinical service provision and health economics.
- To assess fidelity and quality of implementation, acceptability and identify contextual factors associated with variation in outcomes of GAP in order to avoid type III error.

5.3 Trial Design

A cluster randomised trial to investigate whether the GAP package leads to improved ultrasound detection of SGA fetuses. However there is no consensus on the appropriate standard to define SGA. At present, two definitions (population centiles or customised centiles) are being used in clinical practice in hospital throughout the UK. The GROW customised charts, which is one of the

components of GAP programme, has the potential to substantially improve the antenatal detection of babies who are SGA at birth by customized standards. Whilst some of the babies who are SGA by population centiles but not by customised centiles may be detected antenatally by GAP, it is possible that the antenatal detection may be inferior compared to current practice in this group. Furthermore the GAP programme was not developed to identify babies who were SGA by population centiles only. With regards to the use of population chart (routine clinical practice), it is likely that it better detects infants that are SGA by population centiles whilst missing some infants that are SGA by customised centiles. In order to have a common group of infants at risk that should be detected by both intervention in the trial (GAP and routine clinical practice) we propose the use of SGA infant by both customised and population centiles. There is consensus that this group of infants have increased risk of adverse outcomes and evidence suggests these infants are at the highest risk of morbidity/mortality - detection of these babies are crucial. Our trial specifically aims to demonstrate the GAP programme leads to improved detection of SGA at birth by both customised and population centile (primary outcome). To further enhance the interpretation of the primary outcome we will also assess the ultrasound detection of SGA by customised centiles and the ultrasound detection of SGA by population centiles as secondary outcomes. We will also: (i) compare the effect of the intervention on secondary maternal, fetal and neonatal outcomes; (ii) evaluate the implementation of GAP and related economic outcomes; and (iii) explore other ultrasound parameter in the assessment of abnormal fetal growth.

The hospitals participating in the study are not currently using the GAP programme and there is a drive to implement GAP in London in an effort to improve the detection of SGA fetuses with the aim to reduce the incidence of stillbirths. Considering the nature of this intervention, a traditional individual randomized controlled trial is not feasible. Once a unit is trained in GAP it is not possible to randomize their participants to intervention or control due to contamination. A cluster trial is appropriate for the nature of this intervention. Each maternity trust is a cluster in this trial. The clusters will be randomly allocated to either an immediate or delayed implementation of GAP. In the immediate arm training and use of GAP will be instituted (Table 1) at the start of the trial. There will be an interval before the measurement of the study outcomes. This will ensure that in the early implementation arm all deliveries in which the outcome are measured will have been assessed by the GAP programme during the entire pregnancy. This measurement of the outcomes will occur before GAP is introduced in the delayed arm. This will allow comparisons of outcomes between the two arms of the trial.

Table 1. Trial timetable (Gantt Chart).

	2016			2017												2018												
	Pre-trial			Nov-Jan			Feb-Apr			May-Nov						Dec-May *						Jun-Nov						
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Protocol development	X	X																										
Funding application	X	X	X																									
Ethics and R&D approval		X	X																									
Funding activation**					X																							
Randomisation				X																								
Preparation of GAP				X	X	X																						
Early implementation																												
GAP																												
Training							X	X	X																			
Charts used at 12 weeks									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Charts used at delivery																X	X	X	X	X	X	X	X	X	X	X	X	X
Delayed implementation																												
GAP																												
Training																							X	X	X			
Charts used at 12 weeks																									X	X	X	X
Charts used at delivery																												
Data collection / analysis																												
Data collection ***	-	-	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Monitoring study protocol compliance							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Implementation fidelity and acceptability							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Data monitoring							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Statistical analysis																								X	X	X		
Report for funders and manuscript																									X	X	X	
Disseminating the results																											X	X

* If a trust is behind the schedule for participation in the study or implementation of GAP it will start the data collection on month 16 (this will allow for 4 month of data collection as a minimal requirement). ** Funding activation will commence in December 2016 for a period of 24 months. *** Retrospective data collection of women delivering in the pre-trial period will be performed to allow for assessment of completeness of electronic records and baseline data.

6 Methods

6.1 Site Selection

The trial sponsor has overall responsibility for site and investigator selection and has delegated this role to CCTU.

6.1.1 Study Setting

Multicentre study involving antenatal care in the community and hospital maternity units in South East England.

6.1.2 Site/Investigator Eligibility Criteria

Once a site has been assessed as being suitable to participate in the trial, the trial team will provide them with a copy of this protocol.

To participate in the DESiGN trial, investigators and trial sites must fulfil a set of criteria that have been agreed by the DESiGN Trial Management Group (TMG) and that are defined below.

Eligibility criteria:

- A named clinician is willing and appropriate to take Principal Site Investigator responsibility
- Participating site has not implemented the GAP programme

Trial sites meeting eligibility criteria and that are accepted by the TMG as being suitable to recruit to the trial, will be issued with the DESiGN Trial Master File (TMF) documentation to use when applying for Site-Specific Approval (SSA) or local institutional approval as applicable.

6.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The investigator(s) must be willing to sign a CCTU Clinical Trial Agreement or an Investigator Agreement to comply with the trial protocol (confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant trial related duties.

6.1.2.2 Resourcing at site

The investigator(s) should be able to demonstrate a potential for implementing the GAP package in their individual unit which will include cascading of training to all clinical and midwifery staff within the study time line. They should also have an adequate number of qualified staff and facilities available for the foreseen duration of the trial to enable them to conduct the trial properly and safely.

Sites will be expected to complete a delegation of responsibilities log and provide staff contact details.

The site should have sufficient data management resources to allow prompt data return to CCTU.

6.2 Site approval and activation

On receipt of the signed Clinical Trial Agreement or Investigator Agreement, approved delegation of responsibilities log and staff contact details, written confirmation will be sent to the site PI. The trial

manager or delegate will notify the PI in writing of the plans for site initiation. Sites will not be permitted to implement GAP including training until a letter for activation has been issued.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and, by the regulatory authority(ies) (as appropriate), and which was given favourable opinion by the Research Ethics Committee (REC) and/or Institutional Review Board (IRB). The PI or delegate must document and explain any deviation from the approved protocol, and communicate this to the trial team at CCTU.

A list of activated sites may be obtained from the Trial Manager.

6.3 Clusters (Participants)

6.3.1 Eligibility Criteria

As per a cluster randomized trial, all participants eligible for the GAP programme will be eligible for the trial.

Inclusion and exclusion criteria into the study is based on characteristics of the maternity unit (cluster). Hospitals that have fully implemented or will not be introducing GAP will not be eligible for participation.

6.3.1.1 Cluster selection

There will be **NO EXCEPTIONS** (waivers) to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed PRIOR to attempting to randomise the cluster.

Clusters will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined in the protocol.

The strategic clinical network of London and the investigators have written to individual trusts inviting participation in a randomised controlled trial. We have received responses from 12 Trusts that have agreed to participate (table 2). Some Trusts have not yet responded and will be accepted if keen to participate in the trial. There are also some trusts outside London who are keen to participate in the study.

Table 2. Trusts that agreed to take part in the trial.

	Trusts	Birth rate (2013-2014 data)	Agreed to trial
1	London North West Healthcare NHS Trust	4863	YES
2	Chelsea and Westminster Hospital NHS Foundation Trust	5713	YES
3	Guy's and St Thomas' Hospital NHS Foundation Trust	6788	YES
4	Hillingdon Hospitals NHS Foundation Trust	4042	YES
5	Homerton University Hospital NHS Foundation Trust	5877	YES
6	Kingston Hospital NHS Foundation Trust	5763	YES
7	St George's University Hospitals NHS Foundation Trust	4967	YES
8	Imperial College Healthcare NHS Trust	8633	YES
9	University College London Hospitals NHS Foundation Trust	6175	YES
10	West Middlesex University Hospital NHS Trust	4774	YES
11	Royal Surrey County Hospital NHS Foundation Trust	3396	YES
12	Croydon Health Services NHS Trust	3952	YES

6.3.1.2 Cluster Inclusion Criteria

Hospitals that are willing to implement GAP and willing to participate in the trial will be included.

6.3.1.3Cluster Exclusion Criteria

Hospitals that have fully implemented GAP will be excluded from the trial.

6.3.1.4 Eligibility Criteria for Individuals Performing the Interventions

All clinical, midwifery and sonographers providing care in pregnancy.

6.3.1.5 Co-enrolment Guidance

There is no limitation for participants to engage in other individual trials. However, it is expected that hospitals are not involved in other cluster trials investigating similar primary end points (detection of SGA).

6.4 Interventions

6.4.1 Description and components

The intervention is the GAP programme (Appendix 1). The GAP programme is a complex intervention for improved detection of SGA infants through risk stratification, serial fundal height or scans during second and third trimester and use of customized charts for assessment of fetal growth. This programme includes comprehensive staff training and accreditation, evidence-based management protocols, routine monitoring of SGA and detection rates, regular audits of missed cases to help identify training needs and system failures in fetal growth surveillance, and ongoing communication

and support between the Perinatal Institute and Trusts (39). This is a continuous intervention and all these components will be maintained after implementation (except for the initial training). To ensure the intervention was comprehensively described a TIDeR checklist is available in Appendix 2.

The intervention, the GAP programme will be introduced at the level of the hospital (cluster). Clusters randomised to introduce GAP programme will implement training and protocols consistent with principles of GAP (Appendix 1). Women in hospitals randomised to GAP will undergo the following:

- They will be risk assessed for SGA and managed as per GAP protocol. Low risk women will be seen routinely in antenatal clinic. At these visits standardised FH measurements will be performed from 28 weeks. In high risk women serial ultrasounds after 24 weeks will be recommended.
- Customised FH and ultrasound charts will be generated at the first trimester ultrasound visit. FH measurements will be plotted on the customised FH chart. In low risk women any deviation in growth on these charts will result in recommendation for ultrasound measurement. Estimated fetal weight (EFW) from ultrasound measurements will be plotted on customised EFW charts for both low or high risk women whenever an ultrasound is done.

In the delayed implementation arm women will receive routine care as per current hospital practice on screening for SGA.

All components of the intervention are delivered face-to-face to women during their antenatal visits. Number of antenatal appointments needed will vary according to obstetric risk for women in both cluster with or without GAP. Implementation of GAP will not generate additional clinical visits. Risk assessment based on GAP principles will influence schedule of care or antenatal surveillance. Low risk women will not be subject to additional visits or procedures. However, the risk factors or growth abnormalities detected using GAP may trigger the need for additional visits or procedures for clinical reasons.

6.4.1.1 Training & accreditation

The aim is to extend training to all staff engaged in antenatal care. The training will be provided by local trainers who will have received training from the Perinatal Institute. The local trainers will be responsible for cascading the training to multidisciplinary staff in individual units. E-learning and testing packages will also be available to reinforce training and facilitate assessment. Competency documents will be available which will reflect knowledge on fetal growth surveillance and clinical application. There will also be online training and competency logs to internally monitor uptake in the Trusts. The responsibility of training will be reliant on local units. We will assess each unit for trail compliance as per (section 6.4.3)

6.4.1.2 Protocols and guidelines

The GAP offers a protocol template, including evidence-based recommendations to standardise practice in the use of customised growth charts and referral criteria, which clinicians can adapt and integrate in their Trust based protocols. It includes an NHS England algorithm (Figure 1) which is a simplified version of that in the RCOG Green-top guideline for risk assessment and management planning for women in relation to fetal growth surveillance (RCOG 2013) (30).

6.4.1.3 Audit

6.4.1.3.1 SGA rates and detection rates

Routine quarterly reporting of SGA and antenatal detection rates is considered an essential component of the GAP programme to allow accredited Trusts to monitor their performance and benchmark against other units with similar demographics. The GROW software has been enhanced to assist Trusts in the collection of this information and to provide the customised centile at birth for postnatal management. This trial protocol will independently evaluate the incidence of detection of SGA in all births during the pre-specified data collection period in each of the participating units. This will not be reliant on the voluntary data submission by the provider of care after delivery.

6.4.1.3.2 Missed cases of SGA

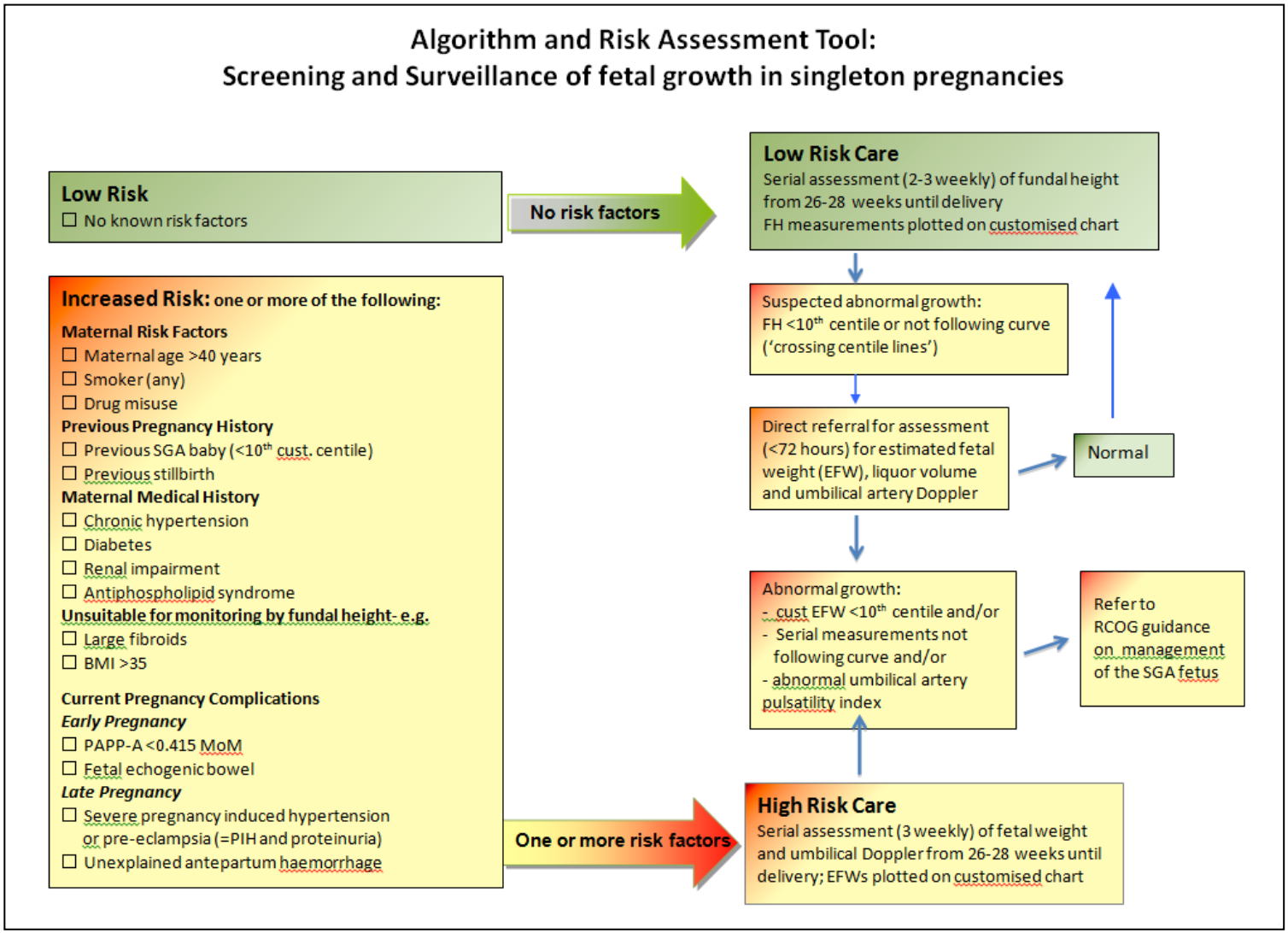
Case reviews have highlighted many learning points for training, protocols and systems failures (40). GAP includes an audit tool to assess local issues relating to fetal growth surveillance. This trial protocol will also independently evaluate the incidence of missed SGA in all deliveries in the pre-specified data collection period within each of the participating units. This will not be reliant on the voluntary data submission by the provider of care after delivery.

6.4.1.4 Support and communication

Based on the programme developed by the Perinatal Institute, Trusts are asked to nominate link persons from each speciality — a midwifery manager (eg head of midwifery, clinical risk manager, matron), an ultrasonographer and an obstetric/fetal medicine lead. These clinicians provide local leadership assisting all aspects of the implementation of the GAP and strengthening the link between their Trust and the GAP team at Perinatal Institute, supporting implementation and feeding back on progress and action plans.

The SCN for London programme team will support regular meetings with the implementation leads to support implementation.

Figure 1. NHS England protocol for screening for SGA fetuses.



6.4.2 Arm A

6.4.2.1 Intervention

GAP programme – this includes: risk stratification according to NHS England algorithm and generation of customised charts at 12 weeks and screening for SGA after 24-28 weeks with FH measurement or serial scans according to stratification of risk in early pregnancy. Customized charts are used as reference for plotting growth assessment (scans or FH measurement).

6.4.2.2 Implementation schedule

Immediate implementation of GAP

6.4.3 Arm B

6.4.3.1 Intervention

Current routine practice – this includes risk stratification according to local policies (if present) and screening for SGA after 24-28 weeks according to local policies (if present). Population charts are used as reference for plotting growth assessments (scans or FH measurement).

6.4.3.2 Implementation schedule

Delayed implementation of GAP (following the data collection period)

6.4.4 Compliance and Adherence

Clusters (hospitals) will be randomized to immediate vs. delayed implementation of GAP. Individual clusters randomised to immediate implementation will receive and cascade the training and start using GAP (Table 1). The GROW web based software automatically calculates compliance of training and implementation of each cluster. The research team will also assess compliance based on number of staff receiving training and the generation of customised charts. The compliance will be checked during implementation so that we can assure that clusters are using GAP before starting the data collection. We will have pre-specified requirements to consider a cluster compliant which consist of assessment of proportion of deliveries using GAP, proportion of staff that completed the online training and confirm local guidelines and audit are in line with GAP recommendations (Appendix 3). Clusters without consistent adherence will be identified and members of Trial Team will meet with the Site PI to discuss strategies to improve compliance with GAP. Clusters not compliant during data collection will be analysed but the non-compliant status will be considered. Compliance will also be monitored during the data collection period.

6.4.5 Concomitant Care

We acknowledge that stillbirth is a national priority and programmes aimed at reducing stillbirth introduced during the period of study may minimise the effect of GAP. There are plans by NHS England to nationally role out a Care Bundle for the reduction of stillbirth. We have discussed the trial with the implementation team in NHS England and at present the date to introduce this care bundle has not been confirmed. The timescales for implementation nationally has also not been confirmed. The GAP programme is also within this care bundle and therefore evidence generated from this trial will provide information on the clinical and health service impact of a national programme. We have discussed with the Strategic Clinical Network in London and the implementation team of NHS England the need for the participating centres in the trial to be exempt from the national programme during the period of the trial.

6.5 Outcomes

6.5.1 Primary Outcomes

The primary outcome will be the ultrasound detection of infants that are SGA (birthweight <10th centile) by both customised and population standards that were detected antenatally after 24 weeks.

* The antenatal charts used for ultrasound detection (numerator) will depend on the allocation arm of the trial. The denominator for the estimation of detection in each arm of the trial will be the same population of SGA infants (SGA by both customised and population).

Table 3. Primary and secondary outcomes and their population

	Study population				
Result of randomised detection method	Not SGA	SGA by customised centiles only	SGA by population centiles only	SGA by both methods	Total
Detected	N1	C1	P1	CP1	T1
Undetected	N0	C0	P0	CP0	T0
Total	N	C	P	CP	T

Primary Outcome:

Detection of SGA by both population and customised centiles: CP1/CP

Secondary outcome:

Detection of SGA by customised centiles: (C1+CP1)/(C+CP)

Detection of SGA by population centiles: (P1+CP1)/(P+CP)

6.5.2 Secondary Outcomes

A. Ultrasound detection of SGA at birth by customised centiles defined as the proportion of SGA infants (birthweight <10th customised centile) that were detected antenatally by ultrasound scan after 24 weeks (us chart allocated by the study arm). We will determine the additional diagnostic test performance (specificity, false positive and false negative).

B. Ultrasound detection of SGA at birth by population centiles (UK90 population centiles) defined as proportion of SGA infants (birthweight <10th population centile) that were detected antenatally by ultrasound scan after 24 weeks (us chart allocated by the study arm). We will determine the additional diagnostic test performance (specificity, false positive and false negative).

C. Effect on short term outcomes

1. Neonatal

a) General - gestational age at birth, birthweight, head circumference
b) Parameters related to immediate condition at birth - 5-min Apgar score <7, delivery with metabolic acidosis (arterial cord ph<7.1), respiratory support in delivery room; parameters related to NICU admission – length of stay, level of care, major neonatal morbidity – one or

more of the following - intraventricular haemorrhage, supplementary oxygen requirements> 28 days, necrotizing enterocolitis, sepsis, retinopathy of prematurity

c) Parameters related to transitional care – length of stay, neonatal morbidity – one or more of the following - hypothermia, hypoglycaemia, nasogastric tube feeding
d) Perinatal loss – stillbirth (antepartum and intrapartum), neonatal death (early and late), death before discharge (after 28 days of birth). In all perinatal losses we will also record cause of death to determine the non-anomalous stillbirth.

2. Maternal

a) Induction of labour
b) Mode of delivery including caesarean section rates
c) Postpartum haemorrhage (>1000ml)
d) Severe perineal trauma -3rd / 4th degree tear
e) Length of stay in hospital
f) Breast feeding at discharge

D. Health economics

a) Number of ultrasound scans after 24 weeks
b) Antenatal clinic / antenatal day unit activity
c) Rates of induction of labour
d) Rates of caesarean sections
e) Length of maternal and neonatal stay
f) Admissions and average length of stay in NICU / SCBU

E. Process evaluation and intervention fidelity

a) Proportion of staff trained
b) Proportion of staff assessed
c) Proportion of women assessed with GAP/GROW programme
d) Missed case analysis
e) Organisational impact and unintended consequences
f) Acceptability and feasibility to women and staff, contextual barriers and facilitators, practice in control sites
g) Adherence to SGA risk stratification and management protocols

F. Other methods of assessments of antenatal detection of SGA:

1. Ultrasound detection of SGA using different threshold (e.g. 5th centile).
2. Clinical detection of SGA at birth (by customised centiles): defined as the proportion of SGA infants (birthweight <10th customised centile) that were clinically detected antenatally (by ultrasound scan after 24 weeks and clinically defined/managed as SGA) in each arm.
3. Growth trajectories (fetal biometry and EFW) and Doppler parameters in the detection of SGA.
4. GROW ultrasound charts (which is single component of GAP) against standard population charts on classification of fetal growth (small for gestational age, appropriate for gestational age, large for gestational age).

6.6 Clusters Timeline

The timeline for clusters was previously described in table 1 and in section 2.1. Hospitals (clusters) will be enrolled and allocated at the start of study. Hospitals that enrol in the study later may be allocated up to 5 month from the start of study. Assessments will be similar in both groups including baseline data collection, data collection throughout implementation followed by assessment of

study protocol compliance (GAP compliance for early intervention and routine care compliance in delayed intervention) and finally data collection on outcomes. The period of assessment of study compliance may be increased to ensure clusters in the early implementation fulfil minimum requirements of GAP programme before the data collection period. The intervention will be implemented in both arms of the trial but at different times. Data collection for outcome measures will be performed during the interval between implementation of GAP in both arms of the study.

6.6.1 Early-Stopping of Follow-up

Criteria will be developed with the TSC/DMC and will be available at the UCL CCTU. If a cluster chooses to discontinue their trial intervention, they should continue to be followed up providing they are willing. They should be encouraged and facilitated not to leave the whole trial, even though they no longer adherent to the intervention schedule. If the cluster exercises the view that they no longer wish to be followed up either, this view must be respected and the cluster withdrawn entirely from the trial. CCTU should be informed of the withdrawal in writing using the appropriate DESiGN trial documentation. Data already collected will be kept and included in analyses according to the intention-to-treat principle for all cluster who stop follow up early. Clusters that stop the trial follow-up earlier than planned will not be replaced.

6.6.2 Participant Transfers

Not applicable

6.6.3 Low compliance of intervention strategy

In the immediate intervention arm, compliance to GAP will be monitored regularly and project midwives will be supported by meetings facilitated by the South London Group programme team. This will include adherence to training protocols, usage of customised charts and protocol development in line with recommendation from GAP (Appendix 3). In hospitals with low compliance the trial team will meet with the site investigator to develop strategies to improve compliance.

6.6.4 Trial Closure

The end of the trial will be 6 months after the last day of the data collection period. This is expected to be the end of month 25 of the trial (Table 1).

6.7 Sample Size

The power of the study is determined by the number of clusters (hospitals), mean size of clusters, intracluster correlation coefficient (or coefficient of variation between clusters), duration of data collection and prevalence of outcome.

Based on the annual number of deliveries in a sample of London Maternity Trusts, we assessed the mean births per year for 12 Trusts that are likely to participate in the trial (5053 births/year). During the data collection period (4 months) a mean of 42 SGA by customised centiles only; 42 SGA by population centiles only; and 126 SGA by both definitions are anticipated per cluster assuming that 12.5% of newborns are SGA by either definition (see distribution on Table 4). This represent a 60% overlap (126/210=60%) and in the unlikely event of a 33% overlap (assuming fixed a SGA rate of 10% by each definition), a mean of 84 SGA by customised and population centiles would be observed. At present in most units data on ultrasound detection of SGA is not routinely collected therefore we based our power calculation on data from the literature. The literature suggests that whether population or customised centiles are used to define SGA at birth, around 20% of SGA births are

detected antenatally by ultrasound (7, 8, 41). We therefore assumed for our sample size the detection rates seen below in table 4 in the delayed arm. For the early implementation arm this represents an improvement in detection of SGA by both customised and population centiles from 20% to 33% (double the Odds Ratio) which we considered clinically meaningful (table 4).

For the additional main outcome we assume detection of SGA (at birth by population centiles) in the delayed implementation group is 20% and in the early implementation group is 28% (Table 4). We select a non-inferiority margin of 5% corresponding to demonstrate the intervention leads to SGA detection of at least 15%.

Table 4. Expected number of SGA and performance of outcomes

	SGA by population only	SGA by both	SGA by customised only	Primary outcome	Additional Main outcome
Total observations*	250	750	250		
Detection – delayed arm (%)	20%	20%	16%	19%	20%
(N)	50	150	40	190	200
Immediate implementation arm GAP (%)	12%	33%	33%	33%	28%
(N)	30	250	83	333	280

* Considering a population of 10,000 babies and SGA distribution according to pooled estimates of previous studies (16, 42-44)

We were unable to identify reports of intracluster correlation coefficient for clinical detection of SGA therefore coefficient of the most approximate outcome, fetal growth restriction, was used (0.019) (45). This leads to a design effect of 4.17 and effective sample size of 242 SGA newborns (by customised centiles, or equally for population centiles) in each study arm. The effective sample size for SGA by both customised and population centiles is 145 SGA newborns.

Based on these assumptions for the primary outcome and the expected 60% overlap between definitions, our study will provide 84% power to demonstrate superiority of GAP in detecting the SGA infants by both customised and population centiles. In a very extreme scenario of an overlap of 33%, our still will still have 79% power to demonstrate GAP improves the detection of SGA infants by both customised and population centiles.

We also performed power calculation for two secondary outcomes. This sample size will also provide 91% power to demonstrate a superiority of GAP in detecting SGA by customised centiles and leads to 92% power to demonstrate non-inferiority of the intervention for the ultrasound detection of SGA by population centiles.

The precision of our power/sample size calculation is limited by the unknown values of the “true” intracluster correlation coefficient for detection of SGA. However, we were conservative in our other assumptions. Prevalence of SGA by customised centiles is around 13-15%, and we are assuming a prevalence of 10%. Also, previous papers have reported a greater difference in detection of SGA

than doubling the OR (primary outcome). These conservative assumptions will allow some variation in the ICC.

6.8 Recruitment and Retention

6.8.1 Recruitment

We have identified 12 clusters (trusts) that are willing to participate in the trial. We are also seeking to increase the number of clusters to reduce the risk associated with loss of follow up.

6.8.2 Retention

The trial team will establish contact with a local site investigator for each cluster. Regular meetings throughout the period of study will be arranged to ensure compliance of the intervention and data collection throughout the study period. There will be regular email and newsletter updates to the participating clusters.

6.8.3 Support mechanisms for interviewed women

Women will be approached initially by research midwives employed by Trusts, and if they agree, their contact details will be shared with study researchers with a view to inviting them to take part in an interview. Research midwives are trained to consider the context of recruitment carefully, and will liaise with senior staff at antenatal clinics to ensure that women are not approached at a time when they are distressed or experiencing negative events our outcomes during their pregnancy. SANDS has produced guidance, which advises that communication with women and families should be sensitive, clear and individualised, and we will follow these recommendations in our approach. In the event that women are willing to be interviewed after experiencing a poor outcome, we will ensure the approach encompasses the guidelines above, and that researchers are also adequately trained and supported to undertake interviews in these circumstances, and to signpost participants to support and other resources available to them.

It is reasonable to anticipate that for some respondents, talking through the events of pregnancy or birth may lead to recall of difficult or distressing events, and this is a risk of taking part in the interview. Although this risk is present, the research interviewers' experiences of conducting in-depth interviews will provide them with skills to help manage this aspect of the research. In brief, if the respondent becomes upset during interview, the researcher will be careful to explore whether they agree to continue, and will suggest stopping or suspending the discussion if emotional discomfort is evident. If they prefer to discontinue, the researcher will remain with them until they are feeling better, and will also provide numbers of support services available to them.

Some respondents may feel comfortable during the interview, but could begin to dwell on their experiences afterwards. For this reason, we will offer contact details for (free of charge) support services to all participants, so that the provision of these is available to all respondents. If the researcher still feels any disquiet about any aspect of an interview, they will ask permission to make a courtesy call a week after the final interview, to check whether they (either mother or partner) wish to revisit any parts of the discussion, and the researcher would also discuss this with their supervisor through the research line management system.

6.9 Assignment of Intervention

6.9.1 Allocation

6.9.1.1 Sequence generation

The method of allocation selected was the random permutation of clusters within each of two equally sized strata; clusters are divided in the two strata according to their size (deliveries per year in 2013-2014) and then randomized to either early or delayed implementation.

6.9.1.2 Allocation concealment mechanism

Not applicable.

6.9.1.3 Allocation Implementation

Allocation will be performed by the study statistician at the start of trial. A second allocation for hospitals enrolled after the start of study will be performed up to the 5th month after the study start date. The CI and the trial Team will coordinate with the Perinatal Institute and the individual cluster to facilitate GAP training and will monitor the implementation to ensure all clusters are working towards the timeline of the study.

6.9.2 Blinding

Not applicable

6.9.3 Emergency Unblinding

Not applicable.

6.10 Data Collection, Management and Analysis

6.10.1 Data Collection Methods

Source of data will vary according to the outcome assessed. Most of the data will be acquired from routine hospital data. This will include clinical notes and also electronic records (Table 5). Data obtained manually from clinical notes will be entered into a trial database. The hospital maternity electronic systems which record antenatal, ultrasound, intrapartum and postnatal data will be processed and uploaded into the study database. Neonatal databases will also be accessed for outcome data. Data from these electronic records will be linked to a patient information number (PIN). The data will then be anonymised and centralised at the CCTU. At each local site there will be a record linking the PIN to the hospital ID. This will be stored locally. No patient identifiable data will be stored centrally. Data will be collected throughout the study (Table 1) and used for three purposes: (i) data from the period prior to implementation will be used as baseline data, (ii) data from training period full compliance and usage of GAP will be used for data monitoring (TSC/DMC) and understand implementation of GAP, and (iii) data collection for a 6 month period (minimum 4 months required) will be used to assess primary and secondary outcomes of this study. To allow for the same length of 6 month of data at baseline (i) and at assessment of outcomes (iii), retrospective collection of data (prior to study start date) will be performed. Same approach will be used to assess completeness of electronic registries using data from prior to start of study in order to highlight data fields that need completion.

Table 5. Summary of data collection strategy.

Endpoint	Data collection
Primary outcome	From electronic records - linked data from US Systems & maternity IT systems
Key secondary outcomes	
A and B. Ultrasound test performance	From electronic records - linked data from US Systems & maternity IT systems
C.1. Neonatal morbidity	From electronic records - linked data from US Systems, maternity IT systems, neonatal IT systems and risk register
C.2. Maternal outcomes	From electronic records - data from Maternity IT systems and risk register
D. Health economics	From electronic records - data from Maternity IT systems, neonatal IT systems, appointments database
E. Process evaluation of implementation	Primary data collection, data from perinatal institute
F. Other methods of assessments of antenatal detection of SGA	From electronic records (linked data from US Systems & maternity IT systems) and primary data collection from review of notes (this is only be performed for the SGA infants at birth according to the maternity IT system).

For measurement of primary outcome the SGA infants by both customised and population centiles will be identified using information from the maternity IT system, the bulk calculator of customised centiles provided by the Perinatal Institute and the calculator for population centiles (UK 90). Data will also be obtained from the maternity ultrasound IT systems to determine the ultrasound detection rate of SGA by both customised and population centiles. For the assessment of secondary outcomes related to ultrasound test performance the same approach will be used.

Data for secondary outcomes will be collected from each hospital electronic system. Data will be assessed for completeness. In routine maternity systems, there is mandatory recording on a number of key outcomes such as mode of delivery, onset of labour and breast feeding. For some outcomes such as admission to NICU we will validate our data by reviewing incident reports to local clinical risk committees. The validity of data collection for trial outcomes will be assessed during the baseline data collection period. Data on many of the neonatal outcomes will be identified from Badgernet which has widespread use in UK (above 90% of hospitals).

For health economic evaluation, data on service provision will be collected which will include length of stay, antenatal clinic appointments, antenatal day unit visits and number of ultrasound. These data will be collected from the hospital appointment systems and ultrasound software.

For process evaluation of implementation, quantitative data includes: proportion of staff trained, staff assessed; women assessed with GAP/GROW programme; adherence to SGA risk stratification and management protocols, missed case analysis data will be gathered from routine data collection by perinatal institute throughout the period on the intervention. Qualitative methods will be gathered through data collected at six intervention sites which will include: Focus groups at six sites with a purposive sample of Health Professionals (6 per group). In two sites (with early implementation and problematic or delayed implementation based on data return at given timepoint), semi-structured interviews with a purposive sample of Health Professionals in each area

along the care pathway (8/site) and semi-structured interviews with a purposive sample of women (10/site). In control sites, interviews with a purposive sample of key stakeholders will elicit current practice (4/site).

For recording other methods of detection of SGA, research midwives will review the maternity notes of SGA infants to identify the number of clinically detected SGA by study criteria. This approach will be used in both arms of the study and will provide the clinical detection rate of SGA. Additional maternity notes during the study period will also be accessed to review missed cases and aspects of evaluation of implementation. Information will be recorded in the trial database without any personal identification.

For assessment of GROW component, data will be obtained from link registries of maternity and ultrasound systems and will provide data regarding the ability of ultrasound to detect SGA fetuses. This antenatal detection will be performed for both population and customised centiles and will test their performance as a diagnostic test (sensitivity, specificity, false positive and false negative rates).

Information from the clusters will also be collected. This will include characteristics such as size of the cluster, ethnic predominance, description of socioeconomic level of population level of complexity of care, number of midwives, number of sonographers, number of consultants, presence of consultants in birth centre, rates of stillbirth and any specific pathway of antenatal care different from standard recommendation (ie. routine 3rd trimester ultrasound).

6.10.2 Data Management

Data will be entered in the approved DESiGN trial database by a member of the DESiGN trial team at local sites and protected using established CCTU procedures.

Coded data: Participants will be given a unique trial Participant Identification Number. Data will be entered under this identification number onto the central database stored on the servers based at CCTU. The database will be password protected and only accessible to members of the DESiGN trial team at CCTU, and external regulators if requested. The servers are protected by firewalls and are patched and maintained according to best practice. The physical location of the servers is protected by CCTV and security door access.

The database and coding frames have been developed by the Clinical Trial Manager in conjunction with CCTU. The database software provides a number of features to help maintain data quality, including; maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data.

After completion of the trial the database will be retained on the servers of UCL for on-going analysis of secondary outcomes.

The identification, screening and enrolment logs, linking participant identifiable data to the pseudoanonymised Participant Identification Number, will be held locally by the trial site. This will either be held in written form in a locked filing cabinet or electronically in password protected form on hospital computers. After completion of the trial the identification, screening and enrolment logs will be stored securely by the sites for 5 years unless otherwise advised by CCTU.

6.10.3 Non-Adherence and Non-Retention

Data on reasons of non-compliance to implementation schedule and withdrawal from the trial will be recorded in the study database.

6.10.4 Statistical Methods

6.10.4.1 Statistical Analysis Plan

A full SAP will be prepared at the start of the study. The key principles include that analysis will be by intention-to-treat. Very little missing data is anticipated for the primary outcome so analysis by complete cases is proposed. All analysis will acknowledge the clustering of individual participants by centre.

6.10.4.2 Statistical Methods – Outcomes

The final decision as to method of analysis will be made once the final number of participating clusters is known. If no more than 12 clusters participate then due to the instability of other approaches, analysis will be by cluster-summary statistic approaches, i.e. calculating the proportion with the primary outcome for each cluster and comparing these values between intervention and control arms using a t-test. This approach includes particular approaches to calculation of effect size and 95% confidence intervals. Should however more clusters participate then more efficient approaches based on an analysis of individual participant data, such as mixed effects models with a random effect for each cluster, will be used which leads naturally to an estimate of effect size (odds ratio for primary outcome) and 95% confidence interval. Subject to the final design for the trial it will be decided whether relevant baseline data are available and if so than an ANCOVA type analysis will be conducted in which adjustment is made for the cluster summary value of the outcome from the baseline period.

6.10.4.3 Additional Analyses - Subgroup

We will assess the effect of the intervention in each of the 4 following groups: SGA at birth by customised centiles only; SGA at birth by population centiles only; SGA at birth by both definitions; and not SGA by both standards. In addition a subgroup analysis of pregnancies at low risk and high risk for delivering a SGA baby will be performed. The definition of risk will follow the proposed in Figure 1.

6.10.4.4 Additional Analyses – Adjusted

As mentioned above adjustment for baseline cluster summary values will be made if these data are collected. Adjustment will also be made for ethnicity. The adjusted analysis will be considered the main analysis.

6.10.5 Analysis Population and Missing Data

The primary outcome is determined only for pregnancies that were SGA by customised and by population centiles, so this forms the primary analysis population. In secondary analysis we will also consider the detection of SGA by ultrasound amongst all birth including those non SGA by either standard. Other secondary analyses such as number of ultrasound scans will also be conducted among all births or amongst specific subgroups as described earlier.

Multiple pregnancies and fetal congenital abnormalities detected before birth are going to be excluded from the primary outcome analysis because detection of SGA in these situations should not be related to GAP or standard care.

6.10.5.1 Economic evaluations

6.10.5.2 Health Economic Analysis Plan

General methodological approach.

A cost-effectiveness (CEA) and cost-utility (CUA) approach to the health economic evaluation will be adopted. For the CEA we will seek to estimate the combined incremental cost of implementing and delivering the GAP programme per additional SGA successfully detected (the primary measure of outcome). The CEA will draw on within trial data generated on patient-levels costs and primary outcomes. It will also account for out of trial long-term resource impacts associated with primary and secondary outcomes observed during the trial, and estimated using economic modelling of adverse health events over extended time horizons.

The CUA take the same approach to cost estimation as with the CEA but will alternatively estimate the incremental cost of the GAP programme per additional quality-adjusted year of gained due to reductions in the risk of still birth that can be indirectly inferred from any observed within trial increase in the rate of SGA detection (impact on still birth cannot be directly measured due to lack of statistical power). The CUA will enable the "value for money" of resources invested in implementing and delivering the GAP programme to be evaluated against existing cost per QALY thresholds adopted by NICE when formulating guidelines and recommendations for funding programmes.

Both the CEA and CUA will utilise within trial data collected as part of the study on resources allocated to implementation activities in the baseline period and data on incremental activities generated by the GAP programme itself and wider resource use arising from maternal and neonatal inpatient hospital stays for patients within the intervention and control sites. All costing of resource use will be conducted at the patient level using existing local and national unit cost estimates.

6.10.5.3 Within-trial analysis

Within trial analysis for the CEA will compare resource use and costs and primary outcomes for participants managed through the GAP programme and participants at the control sites. Within trial cost data will be generated at a patient level drawing on hospital activity data extracted from local NHS data systems and through interviews with stakeholders involved in the implementation process for estimating costing relating to implementation activities over the baseline period (e.g. staff training).

With trial cost-effectiveness (based on the primary outcome measure) will be evaluated probabilistically based on using non-parametric bootstrapping of within trial patient costs and outcomes. A strategy for handling missing data will be discussed and agreed with trial statisticians. We anticipate that the primary within trial economic analysis will be carried using STATA.

6.10.5.4 Model based analysis

The CUA will draw on a combination of within trial data and modelling of out of trial impacts. Epidemiological evidence will be reviewed in order to estimate the change in risk of still birth that would result from the improved detection of SGAs (our within trial primary outcome). Current data on life-expectancy at birth will then be used at a basis for estimating QALY gains from each estimated avoidance of a still birth due to the GAP programme. We will explore alternative sources

of evidence to make plausible assumptions regarding life-cycle health status utility – for example using published EQ5D health status population norms.

In order to capture potential NHS resource impacts of the GAP programme beyond the period of the trial, we will identify the main drivers of long-term impacts in terms of key outcomes observed within trial and review epidemiological and economic evidence and data to model longer-term cost impacts of GAP. Simulation modelling of health impacts (e.g. using Markov methods) will be used to estimate long-term cost impacts relating to gap, with model parameters based on evidence drawn from a review of the relevant literatures.

As with the CEA, we make a probabilistic assessment that the intervention is cost-effective based using existing NICE thresholds and cost-effectiveness acceptability curves.

6.10.5.5 Additional analyses – Evaluation of implementation

The process evaluation, aims to understand the functioning of the intervention by examining implementation, mechanisms of impact, and contextual factors. Implementation of the intervention will be evaluated via a mixed-methods approach drawing on the MRC framework for trials of complex interventions (46, 47). Based on Steckler and Linnan's framework (48), key dimensions of implementation include: **Implementation process** – the structures, resources and mechanisms through which delivery is achieved; **Fidelity** – the consistency of what is implemented with the planned intervention; **Adaptations** – alterations made to an intervention in order to achieve better contextual fit; **Dose** – how much intervention is delivered; **Reach** – the extent to which a target audience comes into contact with the intervention. **Mechanisms of impact** – the intermediate mechanisms through which intervention activities produce intended (or unintended) effects. The study of mechanisms may include: **Participant responses** – how participants interact with a complex intervention.

We will describe the intervention and the mechanisms through which it is expected to produce change in a specific context using the TIDieR guidance and produce a logic model which informs data items for the evaluation of implementation (49). An assessment of each element of the GAP programme will be undertaken (that training and intervention are being delivered as planned and are acceptable according to providers daily work, impact on the clinical pathways that may ensue from the potential increased workloads in referrals, and that contextual influences are understood and addressed).

For process evaluation of implementation, descriptive quantitative information on fidelity, dose and reach will enable us to consider more detailed modelling of variations between participants or sites in terms of factors such as fidelity or reach (e.g. are there ethnic or socioeconomic biases in who is reached?). Quantitative data includes: proportion of staff trained; proportion of staff assessed; proportion of women assessed with GAP programme; adherence to SGA risk stratification and management protocols, missed case analysis data will be gathered from routine data collection by perinatal institute throughout the period on the intervention.

For evaluation of acceptability and feasibility of intervention to staff and women, contextual barriers and facilitators and organisational impact, gathered through qualitative data collected at six intervention sites which will include: Focus groups at six sites with a purposive sample of Health Professionals (6 per group). In two sites (with early implementation and problematic or delayed

implementation based on data return at given timepoint), semi-structured interviews with a purposive sample of Health Professionals in each area along the care pathway (8/site) and semi-structured interviews with a purposive sample of women (10/site). In control sites, interviews with a purposive sample of key stakeholders will elicit current practice (4/site).

6.11 Data Monitoring

6.11.1 Data Monitoring Committee

The joint Trial Steering Committee (TSC)/Data Monitoring Committee (DMC) will meet regularly, as required, to assess any change in maternal, fetal and neonatal outcomes. They will have access to all data available from the trial, including adverse events reported.

Further details of the roles and responsibilities of the joint TSC/DMC, including membership,decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the DESiGN trial TSC/DMC Terms of Reference (ToR).

6.11.2 Interim Analyses

The TSC/DMC will assess adverse outcomes and potential harms of both arms of the trial. The committee will monitor the rates of stillbirth per study arm and per cluster in four months period. An increase of 50% on stillbirth rates in a single cluster will prompt investigation of the site.

No formal stopping rules are planned. Following the Peto Principle (50), the TSC/DMC will recommend that the trial should continue unless the evidence in favour of one treatment is so overwhelming that it would be unethical to continue the trial. A P-value of <0.001 for the primary endpoint (51) may be used as guidance, but the TSC/DMC will be aware of the practical implications of a decision to stop; in particular whether it will make the GAP programme available more quickly or more generally.

These is the suggested approach but the TSC/DMC will decide in their initial meetings if it is appropriate and additional rules for monitoring will be developed. These committees are independent of the investigators and the sponsor and have the rights to decide when to stop or continue the trial.

6.11.3 Data Monitoring for Harm

The non-medicinal intervention being tested in this trial is not expected to have considerable side effects. The intervention is composed of measurement of FH and prompt referral for ultrasound where needed. Side effects of FH may consist of maternal discomfort due to semi-recumbent position and discomfort due to increased sensitivity of skin. Ultrasound is a mechanical wave and can theoretically increase the temperature in the studied tissue. The Doppler ultrasound uses higher energy and focuses in a smaller volume of tissue resulting in greater changes in temperature. In a clinical obstetric scenario, however, the increase in temperature is less than one degree Celsius, which is not considered clinically significant. The World Health Organisation performed a systematic review of 61 publications on the subject and reported no association with adverse maternal, fetal and neonatal outcomes (52). Both components of the intervention are used in different levels on routine care, therefore any of the above cannot be strictly assigned to the intervention.

Other adverse events however can happen due to incorrect use of the GAP tool. This means mistakes in the manual plotting in the FH on GROW chart can lead to an inappropriate management that can ultimately end in a serious adverse event. The audit of missing SGA cases and the review of all stillbirth cases will be performed locally in each cluster as recommended by GAP. Any event associated with misuse of GAP should be reported adverse event in the trial.

The local lead clinician (site investigator) will assess all participants with adverse events and report according to the description below.

6.11.3.1 Safety reporting

Definitions of harm of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply to this trial (Table 6).

Table 6: Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg Investigator's Brochure for an unauthorised product or summary of product characteristics (SPC) for an authorised product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any AE or AR that at any dose: • results in death • is life threatening • requires hospitalisation or prolongs existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect

Adverse events include:

- Missed cases of SGA related to inappropriate plotting on charts or incorrect interpretation of GAP.
- SGA stillbirth related to inappropriate plotting on charts or incorrect interpretation of GAP.
- Maternal death

Adverse events do NOT include:

- Missed cases of SGA associated with lack of resources or delay in achieving the correct management.
- Non-SGA stillbirth.
- SGA stillbirth related to fetal abnormality.
- SGA stillbirth associated with lack of resources or delay in achieving the correct management.

6.11.3.2 Investigator responsibilities relating to safety reporting

All non-serious AEs and ARs, whether expected or not, should be recorded in the patient's medical notes and reported in the appropriate form and sent to CCTU. SAEs and SARs should be notified to CCTU immediately the investigator becomes aware of the event (in no circumstance should this notification take longer than 24 hours).

6.11.3.2.1 Seriousness assessment

When an AE or AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in Table 6. If the event is classified as 'serious' then an SAE form must be completed and CCTU (or delegated body) notified within one working day.

6.11.3.2.2 Severity or grading of Adverse Events

The investigator should make an assessment of severity for each SAE and record this according to one of the following categories:

- **Mild**: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.
- **Moderate**: an event that is sufficiently discomforting interfere with normal every day activities.
- **Severe**: an event that prevents normal every day activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but not severe.

6.11.3.2.3 Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in Table 7.

Table 7: Causality definitions

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely to be related	There is little evidence to suggest that there is a causal relationship (eg the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (eg the participant's clinical condition or other concomitant treatment)	Unrelated SAE
Possibly related	There is some evidence to suggest a causal relationship	SAR

	(eg because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (eg the participant's clinical condition or other concomitant treatment)	
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely	SAR
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

6.11.3.2.4 Expectedness

This relates to adverse reactions and serious adverse reactions and therefore is not required in this non cTIMP trial.

6.11.3.3 Notifications

6.11.3.3.1 Notifications by the Investigator to CCTU

CCTU must be notified of all SAEs within 1 working day of the investigator becoming aware of the event.

Investigators should notify CCTU of any SAEs and other Notifiable Adverse Events (NAEs) occurring from the time of randomisation until 30 days after the last protocol treatment administration. SARs and SUSARs must be notified to CCTU until trial closure.

The SAE form must be completed by the investigator (the consultant named on the delegation of responsibilities list who is responsible for the participant's care) with attention paid to the grading, causality and expectedness of the event. In the absence of the responsible investigator, the SAE form should be completed and signed by a member of the site trial team and emailed as appropriate within the timeline. The responsible investigator should check the SAE form at the earliest opportunity, make any changes necessary, sign and then email to CCTU. Detailed written reports should be completed as appropriate. Systems will be in place at the site to enable the investigator to check the form for clinical accuracy as soon as possible.

The minimum criteria required for reporting an SAE are the trial number and date of birth, name of reporting investigator and sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be sent as soon as it becomes available.

The SAE form must be scanned and sent by email to the trial team at CCTU on **design.trial@ucl.ac.uk**

Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of protocol treatment and/or trial follow-up if necessary. Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to CCTU as further information becomes available. Additional information and/or copies of test results etc may be provided separately. The participant must be identified by trial number, date of birth and initials only. The participant's name should not be used on any correspondence and should be blacked out and replaced with trial identifiers on any test results.

6.11.3.3.2 CCTU responsibilities

Medically qualified staff at CCTU and/or the Chief Investigator (CI or a medically qualified delegate) will review all SAE reports received. In the event of disagreement between the causality assessment given by the local investigator and the CI, both opinions and any justifications will be provided in subsequent reports.

The delegated staff at CCTU will review the assessment of expectedness and, based on possible wider knowledge of the reference material for the treatment or comparator, and after discussion with the CI, may over-rule the investigator assessment of expectedness for the purposes of onward reporting.

CCTU is undertaking the duties of trial sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA and competent authorities of other European member states and any other countries in which the trial is taking place) and the RECs as appropriate. Fatal and life threatening SUSARs must be reported to the competent authorities within seven days of CCTU becoming aware of the event; other SUSARs must be reported within 15 days.

CCTU will keep investigators informed of any safety issues that arise during the course of the trial.

The trial manager or delegate at CCTU will submit Development Safety Update Reports (DSURs) to competent authorities.

6.11.4 Quality Assurance and Control

6.11.4.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the DESiGN trial are based on the standard CCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

6.11.4.2 Central Monitoring at CCTU

CCTU staff will review Case Report Form (CRF) data for errors and missing key data points. The trial database will also be programmed to generate reports on errors and error rates. Essential trial issues, events and outputs, including defined key data points, will be detailed in the DESiGN trial Data Management Plan.

6.11.4.3 On-site Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the DESiGN Quality Management and Monitoring Plan (QMMP). The QMMP will also detail the procedures for review and sign-off of monitoring reports. In the event of a request for a trial site inspection by any regulatory authority UCL CCTU must be notified as soon as possible.

6.11.4.3.1 Direct access to clusters records

Participating investigators must agree to allow trial related monitoring, including audits, REC review and regulatory inspections, by providing access to source data and other trial related documentation as required. Cluster consent for this must be obtained as part of the registration process for the trial.

6.11.4.4 Trial Oversight

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol. Independent trial oversight complies with the CCTU trial oversight policy.

In multi-centre trials this oversight is considered and described both overall and for each recruiting centre by exploring the trial dataset or performing site visits as described in the DESiGN Quality Management and Monitoring Plan.

6.11.4.4.1 Trial Management Team

The Trial Management Team (TMT) will be set up to assist with developing the design, co-ordination and day to day operational issues in the management of the trial, including budget management. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMT terms of reference.

6.11.4.4.2 Trial Management Group

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG terms of reference.

6.11.4.4.3 Independent Trial Steering Committee/ Data Monitoring Committee

The Independent TSC/DMC is the only oversight body that has access to unblinded accumulating comparative data and the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC/DMC provides advice to the CI, CCTU, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC/DMC terms of reference.

6.11.4.4.4 Trial Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. UCL is the trial sponsor and has delegated the duties as sponsor to CCTU via a signed letter of delegation.

7 Ethics and Dissemination

7.1 Research Ethics Approval

Before initiation of the trial at any clinical site, the protocol and any material to be advertised on the prospective clusters will be submitted to the relevant REC for approval. Any subsequent amendments to these documents will be submitted for further approval. Before initiation of the trial at each additional clinical site, the same/amended documents will be submitted for local Research and Development (R&D) approval.

The rights of the participant clusters to refuse to participate in the trial without giving a reason must be respected. After randomisation the clusters must remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they have been allocated. However, the cluster remains free to change their mind at any time about the protocol treatment and follow-up without giving a reason.

Individual women participating in the trial have the opportunity to opt out from the trial so that their data is not used in this study. The Patient information sheet (PIS) has an opt-out section that participants can complete the return to the research team.

7.2 Competent Authority Approvals

This is not a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a CTA is not required in the UK.

The progress of the trial, safety issues and reports, including expedited reporting of SUSARs, will be reported to the Competent Authority, regulatory agency or equivalent in accordance with relevant national and local requirements and practices.

7.3 Other Approvals

The protocol will be submitted by those delegated to do so to the relevant R&D department of each participating site or to other local departments for approval as required in each country. A copy of the local R&D approval (or other relevant approval as above), the PIS and individual consent form must be forwarded to the co-ordinating centre before participants are randomised to the trial. The PIS and the individual consent form are applicable only for the subsample of women participating in the process evaluation interviews. Detailed description of consent for the trial is described in section 7.5.

The protocol has received formal approval and methodological, statistical, clinical and operational input from the CCTU Protocol Review Committee.

7.4 Protocol Amendments

The Trial Team will be responsible to discuss any potential protocol amendment. They will also be discussed with the investigators, sponsors, CCTU, patient groups (SANDS) or other organizations according to the content and how substantive the changes are. The final decision about any amendment will be from the CI and the Trial Team.

Amendments will be submitted for REC approval followed by local R&D approval. Additional approval from other regulatory agencies will be sought where appropriate. All protocol amendments will be communicated to the trial registries and relevant parties.

7.5 Consent or Assent

Investigators conducting individually randomized trials are required to obtain the informed consent of study participants before their random assignment. This ensures adequate explanation about potential risks of intervention and also facilitates the process of randomisation. In cluster randomised trials, however, the size of the cluster may impose a logistic limitation or even make it impossible to obtain individual informed consent and this must be outweighed against the nature of the intervention and potential associated risks (53).

In this cluster randomized trial not only the size of the clusters but an additional temporal issue makes impossible the individual informed consent. Before randomisation of the clusters, prospective women in the trial arm are unknown. Furthermore, the moment a woman presents at a cluster the allocation will have already been assigned. Therefore, the individual does not have the option to withdraw participation and avoid exposure to intervention. In this situation it has been reported the importance of stakeholders, community leaders, decision makers (lead from each cluster) and patient group engagement and agreement with the trial (53). Although it is not the same as individual informed consent, they will be the guardian's of patients' interest before and during the trial. This is in agreement with the MRC recommendations for cluster randomised trial which say that "the roles of the guardians of the patients interests during the trial, the gatekeepers of access to patient groups, and sponsors of the research are even more important in CRTs where individuals may not have the opportunity to give informed consent to participation" (54).

Additionally, is has been suggested the evaluation of a health care programme that is already accepted in clinical practice can be exempted from individual informed consent if clearly justified (55-57). GAP is currently being used in 105 (64%) of Trusts across England (31). Therefore, a harm of the intervention in the clinical detection of SGA should not be expected. As in any clinical trial, the TSC/DMC will also monitor this trial and safeguard the interest of the patient. They are allowed to stop the trial in the case of an unforeseen situation such as any harm related to the intervention.

In view of the above ethical consideration, this protocol has been discussed with key groups in UK. Letter of support from the following group are provided in this protocol: Strategic clinical network (SCN) (Appendix 4), Tommy's (Appendix 5), PPI representative (Appendix 6), RCOG clinical study group on stillbirth (Appendix 7) and SANDS charity (Appendix 8). We have also received a letter of support from NHS England who is currently developing the Stillbirth Care Bundle in which the GAP protocol is one of the four interventions proposed (Appendix 9). Local clinical leads in each cluster will sign the consent for on behalf of the individual participants. The cluster consent form is included in this protocol (Appendix 10).

Finally, the protection of individual participant identification and data has also been considered. This trial follows standard recommendation of confidentiality in which all patient identification will be kept locally. The trial data database and all information stored centrally will be linked to a unique PIN and will not include patient name, hospital number, NHS number or complete address. The trial database will be password protected and safely stored according to CCTU procedures.

Individual consent will be obtained in a sample of women who will be approached for qualitative interviews on the acceptability of the GAP programme. These women will be provided with patient information leaflets and opportunity to consider the participation in the interviews for process evaluation will be provided. The staff of hospital will approached and provided with an information leaflet about the process evaluation study. Individual consent will be obtained from staff taking part on individual interview and focus groups .

7.5.1 Consent or Assent in Ancillary Studies

Not applicable.

7.6 Confidentiality

Participants will be given a unique trial PIN. Data will be entered under this identification number onto the central database stored on the servers based at CCTU. The database will be password protected and only accessible to members of the DESiGN trial team at CCTU, and external regulators if requested. The servers are protected by firewalls and are patched and maintained according to best practice. The physical location of the servers is protected by CCTV and security door access.

Individual data collected manually from clinical notes review will be entered directly into the trial database without any individual identification, such as name, hospital number or NHS number. Data from hospital electronic records will also be linked to a PIN. These data will then be anonymised and centralised at the CCTU in the trial database. At each local site there will be a record linking the PIN to the hospital ID. This will be stored locally. No patient identifiable data will be stored centrally.

7.7 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

7.8 Indemnity

UCL holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant in the clinical trial. UCL does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of UCL or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to UCL's insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to UCL, upon request.

7.9 Finance

The DESiGN trial have a phased funding strategy. Partial funding has already been secured from Tommy's Charity, grant number MQATAVR. Application for additional funding is in place for the GSTT Charity and its timeline is aligned to the study protocol (results in September; planned start of Trial in December).

7.10 Access to Data

The CI and research team for data management and data analyses will have access to data from all clusters. Datasets from all hospitals will be amalgamated by the research team and stored without any patient identification.

7.11 Ancillary and Post-trial Care

No additional care will be required as the individual trusts participating in the trial have undertaken the responsibility of the implementation of GAP in their unit and are committed to continue the use of GAP programme independently after this study. Participating trust may choose to modify their approach to the use of GAP programme following the study. This decision is independent of the trial and will be based on individual trusts clinical strategy.

7.12 Publication Policy

7.12.1 Trial Results

The results of the trial will be disseminated regardless of the direction of effect.

7.12.2 Authorship

The success of the trial depends on a large number of midwives, obstetricians and anaesthetists. Credit for the study findings will be given to all who have collaborated and participated in the study including all local co-ordinators and collaborators, members of the trial committees, the CTU, and trial staff. Authorship at the head of any published paper will take the form "[name], [name] and [name] on behalf of The DESiGN Collaborative Group" and will include specific people involved in each piece of work and the co-investigators.

The writing of the primary results will be the responsibility of a writing committee including all of the investigators. All contributors to the study will be listed at the end of the report, with their contribution to the study identified. Decisions about authorship of additional papers will be discussed and agreed by the trial investigators and advise from the TSC/DMC will be requested if necessary.

7.12.3 Reproducible Research

The trial protocol will be published.

8 Ancillary Studies

This study will offer the opportunity to explore ultrasound patterns of growth in different conditions and to assess the ultrasound detection of LGA. In addition, it will provide the opportunity to explore the epidemiology of other adverse pregnancy outcomes such preterm birth, pre-eclampsia, gestational diabetes, caesarean section, postpartum haemorrhage and neonatal morbidity.

9 Protocol Amendments

Protocol version	Date	Reason for update	Substantial amendment number	Summary of changes
5.0	01/09/2015	Submitted to ethics	NA	Initial protocol.
5.1	13/11/2015	Clarification for ethics	NA	Description of support mechanisms in place for any women interviewed who become distressed
5.1	16/05/2016	Addition for trial documentations	1	Review of PIS and posters as per CAG recommendation
5.1	06/07/2016	Non-substantial amendment 2	NA	Inclusion of 2 new sites.
6.0	14/11/2016	Change outcomes and amendment of PIS and consent forms. Also, update on participating sites, study timeline, data collection, TSC and DMC, planned secondary analysis, authorship, funders and trial registration number.	3	1. Change in outcomes. 2. Clarification of access to data from regulatory agencies on informed consent (they were also removed from the protocol) and clarification of contact numbers in the PIS. 3. Inclusion of a new site; update on previously approved sites; and change of one Principal Investigator. 4. Update study timeline 5. Clarification on data collection and request to collect data retrospectively. 6. Joint TSC and DMC. 7. Inclusion of plan for secondary analysis of collected data. 8. Update on authorship arrangements. 9. Complete funder's info and logo. 10. Inclusion of trial registration and REC number.

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11 Appendices

11.1 Appendix 1. GAP programme description

Growth Assessment Protocol (GAP):

Outline Specification

INTRODUCTION AND BACKGROUND

Fetal growth restriction (FGR) is associated with stillbirth, neonatal death and perinatal morbidity. Confidential Enquiries have demonstrated that most stillbirths due to fetal growth restriction are associated with suboptimal care and are potentially avoidable. A recent epidemiological analysis based on the comprehensive West Midlands database has underlined the impact that fetal growth restriction has on stillbirth rates, and the significant reduction which can be achieved through antenatal detection of pregnancies at risk. Customised assessment of birthweight and fetal growth has also been recommended by the RCOG since 2002 and is re-emphasised in the 2013 revision of the Green Top Guidelines.

The Perinatal Institute (PI) provides tools for assessment of fetal growth and birth weight by defining each pregnancy's growth potential through the Gestation Related Optimal Weight (GROW) software, including

- GROW-chart: customised antenatal charts for plotting fundal height and estimated fetal weight.
- GROW-centile: for calculation of customised birthweight centiles - as an individual centile calculator, or as a bulk centile calculator for databases of pregnancies

The software for these applications has been freely available and used in a variety of settings, and are currently already in use in over 88 trusts and health boards in the NHS as a web application. However recently completed audits in the West Midlands have shown that antenatal detection of fetal growth restriction is directly related to the degree of training and implementation of standardised, evidence based protocols. Therefore from 2013/14, continued or new provision of the software will require Trusts to be accredited in the Growth Assessment Protocol (GAP) Programme. This includes comprehensive staff training, monitoring of FGR referral / detection rates, and regular audits of FGR cases not antenatally detected to help identify system failures in fetal growth surveillance. The GAP programme has resulted in significant reductions in stillbirths in each of the NHS regions where it was widely implemented and has been associated with recent year on year drops in national stillbirth rates in England, to their lowest levels. These successes have been recognised by successive Patient Safety Awards for the Perinatal Institute team in 2013 and 2014.

This document outlines the service specification and agreement the Perinatal Institute proposes to enter with your Trust, with respective roles and responsibilities. It is based on three main elements;

1. Training and accreditation of all staff involved in clinical care
2. Adoption of evidence based protocols and guidelines
3. Rolling audit and benchmarking of performance

GENERAL

The GROW Team at PI would like to establish regular communication with nominated 'link persons' in each specialty, including midwifery (e.g. HOM, clinical risk manager, matron); obstetrics / MFM, ultrasound and IT. These links are intended to serve as conduits for regular communication and feedback on progress.

1. TRAINING

Rationale: Fetal growth restriction is one of the most common complications in pregnancy. Alongside many competing priorities, competency in fetal growth assessment is essential to ensure clinical alertness and ability to make the expectant mother aware that her baby is at increased risk because of suboptimal fetal growth. Standardised assessment improves detection and reduces unnecessary investigations.

Aim: all maternity care providers who are engaged in maternity care to receive instruction on

- awareness of risk factors for FGR and perinatal mortality, including medical, social and obstetric history
- principles and use of customised charts
- standardised fundal height measurement and recording on the GROW chart
- clinical implications and referral pathways

Roles and Responsibilities

PI: - will provide latest updates of the GROW software (stand-alone or linked to the Trust's maternity information system) together with ongoing helpdesk support

- rolling programme of training workshops at the PI for GROW link persons / trainers (dates available at http://www.perinatal.org.uk/diary/diary.aspx)

- provide a GAP e-learning package and competency document to assess trained staff

Trust: - ensures GROW link persons / trainers attend annual 'train the trainers' workshops at the PI
- all staff engaged in maternity care and their supervisors are trained

- ensures competency of staff is assessed

- maintains training and competency log

- all staff complete e-learning package and assessment on an annual basis

2. PROTOCOLS

Rationale: There is currently a wide variation in protocols for risk assessment, fetal growth surveillance and referral pathways. This is often accompanied by insufficient investigations for at-risk

pregnancies as a result of real or perceived shortages in ultrasound services. New national guidelines present an opportunity to implement standardised, evidence based protocols.

Aim: To assist with the implementation of

- risk assessment and definition of low and high risk care pathways at booking / early pregnancy
- indications for serial scans and protocols for frequency and timing
- indications for referral for further investigations / obstetric review where required

Roles and Responsibilities

PI: - will provide template protocols representing the latest evidence for surveillance, referral and investigation of pregnancies suspected of fetal growth problems

Trust: - will agree a Trust wide policy which is consistent with such guidelines

- will monitor and ensure that these are adhered to through regular audit (see 3.)

NB protocols are not intended to replace clinical considerations in the management of individual pregnancies.

3. AUDIT

Rationale: Region wide experience in the West Midlands has shown that 'antenatal detection' of the SGA baby is an auditable indicator and collection of this information itself promotes learning opportunities and improvement.

Aim: To establish a rolling audit programme to monitor performance, through

- the SGA / FGR rate (proportion of babies born with a birthweight below the 10th customised centile)
- rate of antenatal referral for suspected SGA / FGR and antenatal detection/diagnosis of SGA
- regular case-note audit of SGA / FGR cases that were not antenatally detected and action plans in response to system failures

Roles and Responsibilities

PI: - will provide data capture tool to calculate the customised birthweight centile and record antenatal detection of abnormal growth as an integral part of the GROW software

- will provide quarterly reports to feed back and benchmark performance

- will provide a tool and training for case note audit of SGA / FGR cases not antenatally detected

Trust: - will record a customised birthweight centile for each baby

- will record baseline and ongoing referral and detection rates of abnormal growth and set Trust specific targets

- undertake a quarterly case note audit and review of at least 10 SGA / FGR cases not antenatally detected

4. ANNUAL COST

Charges for the Growth Assessment Programme for new GROW users have been calculated on a minimum cost basis and stratified according to number of deliveries. Payment of set-up and pro-rata first-year costs, are due on commencement of training.

Size of Trust births per annum	**Set up cost** Incl. training	**Annual Cost** from 2015/16
<3000	£ 500	£ 1500
3000-5000	£ 500	£ 2000
5000-7000	£ 500	£ 3000
> 7000	£ 500	£ 4000

5. PAYMENT PROCESS

Details for purchase order

Supplier:

Perinatal Institute,
75 Harborne Road, Birmingham B15 3BU
Company Reg: 08466773
VAT: 161-7845-91

Bank:

Perinatal Institute,
NatWest Bank,
Edgbaston
Sort Code: 60-07-41
Account: 51150158

Please return purchase order together with completed Service Agreement, via

E-mail: grow@perinatal.org.uk;
Fax: 0121 607 0102; or
Post: Perinatal Institute
75 Harborne Road, Edgbaston,
Birmingham B15 3BU.

11.2 Appendix 2. TIDieR checklist

TIDieR
Template for Intervention Description and Replication

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	27	
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	20-22	
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	27-31	
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	27-31	
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	27 and 28	
	HOW		

6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	27	
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	27	
	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	27	
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	27	
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	not applicable	
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	31 and 41	
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	31 and 41	

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

11.3 Appendix 3. Minimum requirements for GAP compliance in the DESiGN trial.

Growth Assessment Protocol (GAP) Accreditation

– to follow demonstrable implementation of Training, Audit process and Protocols

1. Multidisciplinary local GAP team identified

- including obstetrician, midwife and ultrasonographer
- links with Perinatal Institute support team
- ensures implementation and Trust ownership of the GAP programme

2. Training:

Content to include

• Awareness of risk factors for FGR and perinatal mortality, including medical, social and obstetric history
• Principles and evidence for use of customised charts
• Standardised fundal height measurement
• Recording on GROW charts including referral guidelines

Completion

At least 75% of staff engaged in maternity care -

- have received face to face training on GAP including
    - principles and rationale
    - fundal height measurement
    - use of customised charts
- completed competency assessment
- completed the e-learning package

• Training log of all staff is monitored and maintained
• On-going training of GAP elements is included in Trust Training Needs Analysis (TNA)

3. Audit:

Content to include:

• Baseline audit to determine rates of SGA, referral and detection
• Use of GROW application to produce centiles and referral and detection rates
• Missed case audit to examine cases with unrecognised SGA

Completion:

• 3+ months of annual deliveries baseline audit of detection rates completed using the GROW tool
• Process in place to record birthweight and referral & detection after each birth
• Tool in place and staff assigned and trained in missed case audit tool and process

4. Unit or Trust Protocol:

Content to include

• Risk assessment and definition of low and increased risk care pathways at booking / early pregnancy
• Indications for serial scans and protocols for frequency and timing
• Indications for referral for further investigations / obstetric review where required
• Risk assessment at booking/early pregnancy according to NHS England FGR algorithm.

Completion:

Evidence that GAP template protocol tailored to local use and implemented

11.4 Appendix 4. Letter of support from SCN

London
Strategic Clinical Networks

London Maternity Strategic Clinical Network

Dr Dharmintra Pasupathy MSc PhD MRCOG
Senior Lecturer / Consultant in Maternal & Fetal Medicine
and Perinatal Epidemiology
Division of Women's Health
Women's Health Academic Centre KHP
10th Floor North Wing
St. Thomas' Hospital
Westminster Bridge Road
London SE1 7EH

15th July 2015

Dear Dharmintra

Re: The DESIGN trial: a cluster randomised trial to investigate the impact of the Growth Assessment Protocol (GAP) on perinatal outcomes

As Co- Clinical Director of the London Maternity Strategic Clinical Network I am writing in support of the DESIGN trial and to thank you for taking on its leadership. When the network was initiated we identified reduction of the high stillbirth rate in London as being a priority outcome. There is a body of mainly observational data to suggest that the GAP protocol may help us meet this outcome but we are also aware that the evidence base has been questioned at a national level and that there is an urgent need to perform a randomised study to address this. We are delighted that the natural process of implementing GAP in London units can be used to support this trial and are pleased to have been in a position to contribute to the design and concept underlying this important study.
We look forward to working with you and your team to implement the DESIGN trial in a timely manner.

Best wishes

Professor Donald Peebles
Co Clinical Director of the London Maternity Strategic Clinical Network

11.5 Appendix 5. Letter of support from Tommy's Charity.

www.tommys.org

Dr Dharmintra Pasupathy MSc PhD MRCOG
Senior Lecturer / Consultant in Maternal & Fetal Medicine and Perinatal Epidemiology
Division of Women's Health Women's Health Academic Centre KHP
10th Floor
North Wing
St. Thomas' Hospital
Westminster Bridge Road
London
SE1 7EH

6th July 2015

Dear Dr Pasupathy,

I am writing in support of the need for a trial to evaluate GAP (DESiGN trial); as far as I know, no comprehensive study has been conducted to assess the effectiveness of this intervention and the impact on clinical services. This is our only opportunity to evaluate this intervention before it is rolled out to all hospitals in England. Those who have already implemented GAP report mixed results with some significant concerns being expressed.

Tommy's support the methodology, of hospital based randomisation and would consider it to be a robust and cost effective way to evaluate the intervention.

Yours sincerely,

Jane Brewin
Chief Executive

0207 398 3450
jbrewin@tommys.org

Tommy's
Nicholas House
3 Laurence Pountney Hill
London EC4R 0BB

Tel: 0207 398 3400
Fax: 0207 1983476
Email. info@tommys.org
Web: www.tommys.org

Registered charity no 1060398 and SC039280

Tommy's

11.6 Appendix 6. Letter of support from PPI representative.

Personal support to the proposed randomised trial for GAP – London, 18th July 2015

Dear Sirs,

Following the death of my daughter Liberty Rose in January 2011, due to severe and undetected FGR, I have been since campaigning, fundraising and supporting charities and organisations working to prevent so many avoidable deaths every year.

Despite the good progress of the last couple of years, I believe the UK is still a long way away from the standards that we would expect and demand. There is consensus that up to 1,000 FGR stillbirths per year could be prevented by radically improving our standards of antenatal care.

From what I've learnt in the last four years, I believe the widespread adoption of GAP across the country would significantly contribute to reducing preventable FGR stillbirths. In this context, the proposed randomised trial is in my opinion a very important step along the journey of introducing simple, cost effective measures to save so many innocent lives, like Liberty's.

The trial, with its proposed approach, seems to me, within the limitation of my technical competencies, sensible and pragmatic and I would sincerely hope that it can be rapidly implemented in the proposed timescales.

Kind regards,

Alessandro Alagna

Email: alessandro.alagna.uk@gmail.com

Mobile: 07950 345 274

11.7 Appendix 7. Letter of support from RCOG clinical study group on stillbirth.

UNIVERSITY OF CAMBRIDGE
Department of Obstetrics and Gynaecology

Gordon C S Smith MD PhD DSc FRCOG FMedSci
Professor of Obstetrics & Gynaecology
Consultant in Maternal-Fetal Medicine
Head of Department

8th July 2015

Dr Dharmintra Pasupathy
Division of Women's Health
Women's Health Academic Centre KHP
Guy's & St Thomas' NHS Foundation Trust
King's College London
10th Floor North Wing
St Thomas' Hospital
London SE1 7EH

Dear Dharmintra

Re: The DESiGN Trial: a cluster randomised controlled trial to evaluate the effect of the Growth Assessment Protocol (GAP) on perinatal outcomes

Thank you for presenting your proposal to the Stillbirth Clinical Study Group (CSG) of the Royal College of Obstetricians and Gynaecologists.

We discussed the aims of your study and the proposed methodology and we are in agreement that the effectiveness of this intervention does need robust independent evaluation. The current evidence base is only observational and your cluster RCT will achieve this. It will also provide additional information on the impact of GAP on maternity service provision. The findings of this study have the potential to inform future national strategies to improve the detection of small for gestational age infants and stillbirth.

We support the current methodology proposed which has incorporated the feedback from the CSG.

I hope this important study can proceed expeditiously and look forward to hearing the results.

Yours sincerely

Professor Gordon C S Smith

Athena SWAN Silver Award

Box 223, The Rosie Hospital
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Cambridge, CB2 0SW
Tel: +44 (0)1223 336871
Fax: +44 (0)1223 215327
paosmdghod@medschl.cam.ac.uk

11.8 Appendix 8. Letter of support from SANDS charity.

Sands
Stillbirth & neonatal death charity

3rd Floor 28 Portland Place
London W1B 1LY
t: 020 7436 7940
e: info@uk-sands.org
www.uk-sands.org

Dr Dharmintra Pasupathy

14 August 2015

Dear Dr Pasupathy

Re: proposed *DESiGN* trial: *Detection of small for gestational age fetus (SGA) – a cluster randomised controlled trial to evaluate the effect of the Growth Assessment Protocol (GAP) programme*

Thank you for your proposal, which was considered by the Sands Board of Trustees on 25 July 2015. I am very pleased to say that the Board are very supportive of your proposal and have agreed to provide £40,000 as a one off grant in the 2015/16 financial year towards the costs of the DESiGN trial. This funding is subject to your securing the remainder of the funding required. We would also aim to agree final terms of the funding agreement before the study starts, which we understand you aim to do in September 2015.

We understand that the study will run for 15 months, with a further period to analyse and write up the data. As part of the funding agreement we would require an interim report after 12 months and final report on completion of the study.

Yours sincerely

Judith Abela

Judith Abela
Head of Operations &
Interim Deputy Chief Executive

11.9 Appendix 9. Letter of support from NHS England.

NHS England

Medical Directorate,
NHS England,
6A Skipton House,
80 London Road,
London,
SE1 6LH

Dr Dharmintra Pasupathy MSc PhD MRCOG
Senior Lecturer / Consultant in Maternal & Fetal
Medicine and Perinatal Epidemiology
Division of Women's Health
Women's Health Academic Centre KHP
10th Floor North Wing
St. Thomas' Hospital
Westminster Bridge Road
London SE1 7EH

19 July 2015

By email

Dear Dr Pasupathy,

Re: The DESiGN Trial: a cluster randomised controlled trial to evaluate the effect of the Growth Assessment Protocol (GAP) on perinatal outcomes

Thank you for keeping me updated on the development of the aforementioned study.

As you know, and indeed experience as a frontline clinician, England is unfortunately one of the worst performing countries in terms of stillbirth and indeed neonatal deaths, in Europe / high income countries.

NHS England has always relied on the expertise of others to shape national clinical policy through evidence, and of course the "Why children die" study by a Guy's and St Thomas' NHS FT colleague, Dr Ingrid Wolfe et al, has highlighted once again the gap in performance between England and other countries.

NHS England is therefore mandated by the Government to reduce stillbirths and we have been leading the development of a care bundle for reducing stillbirth and early neonatal death. This approach was indeed influenced by the success of other care bundles, including the GSTT Charity funded - AMBER.

Our Saving Babies' Lives care bundle is tackling smoking as well as labour-related clinical processes, but the one element we consider key for its success is focusing on appropriate measurement of the size of the fetus, recording thereof and subsequent use of the right process to manage the pregnancy. This element of the care bundle, **Identification and surveillance of fetal growth restriction**, is based on the existing but limited evidence of what works for this type of stillbirths, a great proportion of which we believe to be avoidable.

One way of delivering identification and surveillance of fetal growth restriction, is through the GAP programme and therefore your study is of great interest to us. We are unfortunately limited in funding in the national team but would certainly consider

supporting your work if we could. Hence, I am very happy to support your funding application as it will help increase the evidence base both in terms of outcomes as well as service impact. The findings of your study will add significantly to the current evidence base that is available which is primarily only from observational studies. The results of your study will certainly also inform the strategy of implementation of the stillbirth care bundle nationally.

In the past, I have directly delivered improvement for the people in Lambeth and Southwark through a GSTT Charity - funded programme (Diabetes Modernisation Initiative) and I therefore have every confidence that the Charity will consider this application for its true merit.

I do hope you are successful in your funding application so that this important study can proceed.

Thank you,

Dimitri

Dr Dimitri Varsamis
Programme Manager

Acute Care Clinical Policy and Strategy Unit
Medical Directorate
NHS England

High quality care for all, now and for future generations

11.10 Appendix 10. Cluster consent form from local clinical leads.

Dr Dharmintra Pasupathy MSc PhD MRCOG
Senior Lecturer / Consultant in Maternal & Fetal Medicine
and Perinatal Epidemiology
Division of Women's Health
Women's Health Academic Centre KHP
10th Floor North Wing
St. Thomas' Hospital
Westminster Bridge Road
London SE1 7EH

DATE

Dear Dr Pasupathy

Re: Invitation to participate in the DESiGN Trial

Thank you for the invitation to participate in the DESiGN Trial, a randomised controlled cluster trial.

On behalf of our maternity unit and clinical director of maternity services, *PLEASE ADD NAME OF HOSPITAL* we agree to participate in this trial. This trial has been discussed in our unit and I *PLEASE ADD YOUR NAME* am the nominated clinical link in our unit for this study.

Our participation is based on the consensus that this is an area that needs to be robustly evaluated through a randomised controlled trial before implementation. An understanding of the impact on detection, clinical outcomes and service provision is crucial. We understand the study design and the implication of our participation.

We acknowledge and agree that based on the nature of this study, hospitals will be randomised to either early or delayed implementation of GAP. We understand that consent for participation of this study is at the level of the maternity unit and not individual patient based consent.

Best wishes

YOUR NAME & SIGNATURE