$50M Wellcome Leap Program
In Utero: Measurement and modelling during gestational development

Every 16 seconds one baby is stillborn. That amounts to more than two million stillborn babies globally every year. Stillbirths have long-lasting personal and psychological consequences for parents, as well as substantial costs for wider society.

“Experiencing a stillbirth during pregnancy or childbirth is a tragedy insufficiently addressed in global agendas, policies and funded programmes. There are psychological costs to women, especially women, and their families, such as maternal depression, financial consequences and economic repercussions, as well as stigma and taboo.”

- World Health Organization

The internationally recognised classification of a stillbirth is a baby who dies after 28 weeks of pregnancy, but before or during birth.

Early recognition of emerging complications in utero, coupled with timely and safe delivery, is estimated to have the potential to reduce the number of stillborn babies by half. Yet progress to reduce stillbirth remains stubbornly slow. In sub-Saharan Africa headway in reducing stillbirth rates has been outpaced by growth in the total number of births, so stillbirth numbers are actually rising. In the USA stillbirth rates have been static for more than a decade, which amounts to a total of 12,000 stillborn babies each year. Every child’s death is heartbreaking, and this number of stillbirths is ten times higher than the annual number of deaths from childhood cancer.

Worldwide, great strides are being made in reducing the number of baby deaths that occur after birth, but reductions in baby deaths that occur before birth (stillbirths), are lagging behind. Globally, in the year 2000 there was 1 stillbirth for every 3 newborn deaths in the first month of life. By 2019, in nearly 50 countries that ratio was more than 1 to 1. For some babies, remaining in utero is higher risk than being born, largely because in utero, life-threatening complications can develop and progress undetected. Our goal is to be able to measure, model and predict gestational development, with a primary focus to reduce stillbirth rates by half. To achieve this we need non-invasive, scalable ways to assess gestational development in utero.
Stillbirth is the endpoint of a number of different processes that involve the mother, baby, or the placenta – or a combination of the three. The placenta is the life support system of the developing baby. In humans, the placenta couples the separate maternal and developing baby’s circulations to allow transfer of oxygen and nutrients from mother to baby. This placental transfer function is influenced not only by placental size and structure but also by the integrity of the maternal circulation through the uterine vasculature; and adequate circulation through the umbilical cord for the baby. The placenta is also itself metabolically active and secretes bioactive substances and hormones that influence the maternal response to accommodate pregnancy, whilst acting as a barrier to substances, such as viruses and certain drugs, that may damage the developing baby.

The lack of methods to assess gestational development in utero limits our ability to predict the risk of stillbirth. Today 25-50% of stillbirths are unexplained - meaning that no conditions that affect the mother, baby, or placenta that could contribute to the baby’s death are identified. Even in cases where possible contributory conditions are found, it is extremely rare to have sufficient resolution on the sequence, timing and exact mechanisms leading to stillbirth. Such inadequate basic understanding restricts opportunities to advance preventative treatments. By developing new measures and models of gestational development, we also will identify new opportunities to prevent stillbirths.

To date, characterisation of gestational development has relied on intermittent, indirect measures. For example, ultrasound assessment of the baby’s growth and/or Doppler assessment of blood flow in the umbilical cord, are often performed weeks to months apart. These tests have poor predictive performance for the risk of stillbirth. Being able to measure and integrate maternal, baby and placental signals, daily or even more frequently, is central to characterising gestational development and is likely key to preventing stillbirth.

Why now?

Advances in mobile sensing technologies and optical imaging, coupled with advances in data analytics, provide opportunities to assess placental function, maternal response and baby’s behaviour in utero, in real time, at greater resolution than ever before. For example – moving from weekly subjective assessment by healthcare practitioners in clinics, to remote, hourly objective assessments of in utero activity could detect acute reductions in oxygen supply to the baby, that if not acted on, may cause stillbirth within a few hours.
In addition, rapid non-invasive analysis of material from the placenta and the developing baby is becoming a reality through analysis of cell-free nucleic acids, placental vesicles, and exosomes that circulate in the mother’s blood; the use of ‘omic’ platforms can detect novel biomarkers of gestational health and disease; and advanced high-resolution *in vivo* (e.g. MRI) and *ex vivo* (e.g. microCT) imaging coupled with mathematical modelling, can add new insights into the characterisation of placental transfer functions.

No animal models replicate the large size and unique structure of the human placenta. However, animal studies have helped to elucidate a developing baby’s responses to oxygen and nutrient restriction. These studies indicate there may be opportunities in human pregnancy for recognition of evolving complications, providing opportunities for intervention. In particular, a developing baby’s response to inadequate placental oxygen and nutrient transfer includes changes in heart rate, blood flow patterns, growth trajectory and behaviour. In response to acute lack of oxygen (triggered, for example, by compression of the umbilical cord), there is a reduction in a developing baby’s heart rate from the normal baseline (in humans at term, 120 -150 beats per minute) of ≥15 beats per minute; which may be followed by compensatory increases in heart rate if oxygen restriction persists. In response to a lack of oxygen, the developing baby also stops performing breathing-like movements (rapid, 1-4Hz episodic movements occurring 30-40% of the time after 30 weeks gestation) and the normal cycle of *in utero* sleep and wakeful periods is affected, with a resulting reduction in the baby’s movements.

Tragically, in up to 55% of stillbirths, mothers report a decrease in their baby’s movements in the week before their baby died. Attempts to use the subjective maternal perception of reduced baby movements as an opportunity to increase monitoring and/or expedite birth to reduce stillbirth have been unsuccessful. Accurate and frequent objective measures of *in utero* behaviour of the developing baby, in combination with other measures, hold more promise.

Large observational studies in humans have shown other insights. Pregnant women who fall asleep on their back have a 2.6-fold increased risk of stillbirth. When a pregnant woman lies flat, the uterus can fall backwards compressing her aorta, and inferior vena cava (one of the main veins returning blood to the heart) affecting *in utero* blood flow. This can happen during maternal sleep and has led to recommendations that pregnant women fall asleep on their side rather than their back. There are no proven interventions to promote this practice.
Together these observations and technological advances indicate that there is potential for a step-change in our ability to reduce stillbirths, with integrated measures of maternal, developing baby and placental function that accurately model gestational progression. These could allow opportunities for timely and safe delivery—based on individual risks—to prevent stillbirth.

Effective predictive models of gestational development would also minimise unnecessary, potentially harmful interventions in healthy pregnancies. As the birth of a baby removes their risk of stillbirth, a strategy of intentionally delivering babies before their due date — by induction of labour or planned caesarean section — is increasingly used in attempts to reduce stillbirths. There has been a 40%-60% increase in such healthcare provider-initiated births over the past decade in a variety of settings, with the result that in many countries only around half of births are preceded by spontaneous onset of labour. In the absence of alternative approaches, this trend is understandable.

However, any benefit in reducing stillbirth needs to be carefully balanced against health risks of the infant being born early, even in births close to term. A lack of precision in current risk-based approaches to stillbirth reduction means that many babies are unnecessarily delivered “just in case” of late pregnancy complications. For example, it has been estimated that to prevent a single stillbirth with the now common strategy of offering provider-initiated birth at 39 weeks gestation, more than a thousand women will undergo induction of labour or Caesarean section rather than awaiting spontaneous labour. These provider-initiated births have a substantial burden on maternity services, and may also be harmful to children in the long term, as childhood need for special educational support and behavioural problems are all lowest in babies born at or after their due date.

**Program goal.**

Our goal is to create the scalable capacity to measure, model and predict gestational development, with sufficient accuracy to reduce stillbirth rates by half, without increasing provider-initiated delivery.

**Call for abstracts and proposals.**

We are soliciting abstracts and proposals for work over 3 years (with a potential additional one-year option) in one or more of the following thrust areas. Proposers should clearly relate work in these thrust areas to the program goal.
It is not necessary to form a large consortium or teams to address all facets of the program (see Thrust areas below). The strength of this approach will manifest through program-level integration of efforts from individuals and small agile teams with deep (and sometimes narrow) expertise. Across all projects, Wellcome Leap will facilitate iterative and collaborative integration of findings to refine models and improve and validate predictive measures and adapt approaches as teams make progress together towards shared goals.

**Thrust Area 1: Identification and testing of new measures and biomarkers**

Develop and test new measures and biomarkers that characterise one or more aspects of maternal, placental and developing baby’s gestational development with the potential to be integrated into models that are predictive of the risk of stillbirth (Thrust Area 3); and/or identify or characterise mechanisms of stillbirth with tangible opportunities for intervention to reduce death and disability (Thrust Area 4).

Of particular interest are measures that can be used in remote settings or with a daily turnaround, such as mobile diagnostic technologies, wearables, and optical imaging techniques; circulating biomarkers including but not limited to genome, metabolome, and hormones; and studies that correlate high fidelity, technology-intensive methods and/or mathematical modelling (e.g., functional MRI or high-resolution ultrasound in pregnant women), with low-cost, easily deliverable screening measures.

Representative advances and methods for non-invasive in utero sampling include amniotic fluid sampling equivalents (measuring metabolites in the fluid that surrounds the developing baby without requiring invasive sampling [amniocentesis]), and indirect measures of maternal responses to pregnancy in accessible sites (e.g., assessing maternal vascular responses to pregnancy via retinal imaging).

Studies in humans will be prioritised. Studies of gestational development in large animal models will be considered only if they provide an essential translational bridge to achieve program goals. Studies can be based on novel data and sample collection, or analysis of existing longitudinal data and biological samples from well-phenotyped pregnancies.
Measures can be performed at any stage in pregnancy, but studies relating to the prediction of antepartum stillbirth (after 28 weeks gestation) will be prioritised over studies of methods to monitor babies’ wellbeing in labour.

Tests must provide reliable measurement, as demonstrated in feasibility studies including in at least 40, and up to 1,000 pregnant women. Markers should be verified against birth outcomes. Well defined, objective and clinically meaningful surrogate measures of stillbirth can be used for proof-of-concept studies of the potential to predict risk of stillbirth. Examples include newborn brain injury, signs of newborn compromise (such as metabolic acidosis in cord blood taken at delivery; low [<7 or <4 out of 10] 5-minute Apgar score or newborn hypoglycaemia [low blood sugar]) and/or growth restriction of the baby that meets standardised diagnostic criteria. Definitions will be aligned across the program.

As the majority of stillbirths occur in women with no identified risk factor for stillbirth, studies must include women representative of the general population of pregnant women; but can be enriched with participants with outcomes of interest for biomarker identification.

We are not looking for studies that rely exclusively on postpartum biological samples (placenta, umbilical cord or newborn blood) or data, without correlation to antepartum screening measures. We do not anticipate supporting studies using small animal models due to a lack of fidelity to human placentation and in utero development.

**Thrust Area 2: Pilot novel approaches to data collection**

Create and test opportunities that would enable future testing, validation, and trials of new technologies rapidly and at scale.

Sample sizes in the order of tens of thousands of women are required to trial new measures and biomarkers and models of stillbirth risk. To date, appropriate testing at this scale has been a central limiting factor in the validation of new methods to screen and prevent stillbirth.

We are looking for proposals that clearly demonstrate the potential to generate data and/or biological samples from; or enable efficient clinical trials in, a minimum of 1000 women and their babies. These may include virtual cohorts,
crowd-sourcing approaches and clinical networks that enable platform trials with adaptive designs, or cluster trials.

Proposals developing capabilities that would enable possible future data collection from 10,000+ women and babies will be prioritised. It is not anticipated that studies of this scale will be performed within the scope of the In Utero program. However, we are interested in building and testing capabilities for future rapid data generation - e.g., proof-of-principle studies linking data from mobile phones and wearable devices to routinely collected healthcare data or existing pregnancy cohorts.

Approaches and teams must have the capacity and willingness to be flexible and pivot (within weeks) to include new measurements (e.g., the inclusion of new digital biomarkers); and/or allow longitudinal sample collection (e.g., maternal blood samples coupled with placental samples collected at delivery) according to standardised protocols which align across the program to enable analyses by different testing modalities (e.g., proteomics, metabolomics). Clinical and experimental data and biological samples must be able to flow between (or, in the case of data, be accessed remotely by) relevant researchers within the program for analysis. Demonstrable evidence of how this can be achieved within governance frameworks and privacy regulations should be provided.

**Thrust Area 3: Development, integration and validation of predictive models of gestational development**

Develop models of gestational development (from 28 weeks onwards), based on measures identified in Thrust 1, and then iteratively test, refine and validate it in cohorts from Thrust 2. State-of-the-art techniques will be used, recognising that different types of models may be necessary to provide understanding of different aspects of gestational development. Our intention is that sub-models will interconnect and combine into an overall predictive model.

As such, we are looking for teams with the ability to leverage the latest computational techniques, including machine learning methods, as well as the ability to develop and integrate models using different computational techniques. We anticipate that individual and, eventually, integrated models will be exercised at regular intervals (every six to nine months) during the performance period. Output and learning will then be fed back into the program...
to both inform ongoing work in Thrusts 1 and 2, and flag new areas for investigation.

**Thrust Area 4: Methods for scalable screening, prevention and intervention**

Create novel measurement tools that can be widely deployed without specialist training, and enable collection of data throughout gestational development. Technologies should have the potential to be scalable across different geographical and cultural settings.

Of particular interest are wearables that remotely monitor aspects of in utero behaviour (e.g., babies’ movements, babies’ breathing) and/or physiology (e.g., babies’ cardiac cycle) with built-in alerts to attend for medical review if abnormalities are detected. We are also seeking methods that can be used to confirm normal placental transfer function in pregnancies at or around term, to rule out the need for provider-initiated birth to reduce the risk of stillbirth.

Proposals relating to sleep monitoring are also welcome. For example, proposals to develop sensors that can accurately detect a reduction in maternal oxygenation (e.g., from sleep apnoea), or compromise to in utero oxygen and nutrient supply due to sleep position (from compression on maternal blood vessels) with stimuli to change position if these are compromised. These might include sensors in mattresses or non-invasive sleep monitors with feedback capabilities.

To ensure that they are fit for purpose, new technologies should be designed with input from pregnant women early in, and frequently throughout, the development process.

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**REFERENCES:**


