LIFE STUDY | Understanding lives – now and for the future

# Life Study Scientific Protocol


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## Forward

The Life Study protocol was developed by the scientific leadership team together with experts from a wide range of disciplines drawn from the biomedical, clinical and social science research communities who formed part of a wider affiliated scientific network. The protocol sets out the key research themes of the study, chosen to capitalise on the unique opportunities afforded by the Study design, and to enable a wide range of research questions and policy issues relevant to children to be explored.

The Life Study protocol was initially developed in response to the call specification for bids for a leadership team for a new birth cohort study issued by ESRC and MRC in 2009. This call specification was informed by preceding reviews commissioned from Longview by the ESRC between 2006 and 2009. Following international peer review and interviews by an international panel, ESRC awarded funding to the proposal from the leadership team led by Professor Dezateux. Funding was not released until 2011.

The Life Study protocol was developed by members of the Scientific Protocol Development Group with input from Scientific Working Groups, each co-chaired by social and biomedical scientists. Ad hoc subgroups and external experts contributed on focussed aspects. A public consultation took place on the draft protocol in July 2012, followed by an independently conducted web survey with input from a wide range of disciplines. The Life Study Scientific Steering Committee (members listed below) is responsible for the content of this protocol, having approved its final content and any revisions needed in the light of experience following piloting. They, and key members of the Life Study team, are its authors.

This document sets out the Life Study protocol, approved by the Research Ethics Committee in January 2015 when the first Life Study Centre opened and which was in operation at the time the decision to close Life Study was taken by the funders in July 2015.

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Special thanks are extended to Professor Paul Burton – formerly a member of the Scientific Steering Committee – for his expert contributions to the initial proposal and the final protocol in respect of power and sample size calculations.

The support of the Centre for Facilitation in using consensus methods to review and prioritise the questionnaire content is gratefully acknowledged.

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## Abbreviations

| | |
|---|---|
| ALSPAC | Avon Longitudinal Study of Parents and Children |
| BHRUT | Barking, Havering and Redbridge University Hospitals Trust |
| CAG | Confidentiality Advisory Group |
| DLES | Data Linkage and Extract Service |
| DfE | Department for Education |
| DWP | Department of Work and Pensions |
| EAG | Ethics Advisory Group |
| EAGDA | Expert Advisory Group on Data Access |
| EIG | Ethics and Information Governance |
| ESRC | Economic and Social Research Council |
| HFEA | Human Fertilisation and Embryology Authority |
| HSCIC | Health and Social Care Information Centre |
| HRA | Health Research Authority |
| ICH | Institute of Child Health |
| ICO | Information Commissioner's Office |
| LSSAC | Life Study Strategic Advisory Committee |
| MoBA | Norwegian Mother and Child Cohort Study |
| MCS | Millennium Cohort Study |
| MRC | Medical Research Council |
| PPI | Participant (Patient) and Public Involvement |
| REC | Research Ethics Committee |
| SPDG | Scientific Protocol Development Group |
| SSC | Scientific Steering Committee |
| SWG | Scientific Working Groups |
| ONS | Office for National Statistics |
| UCL | University College London |
| UCLH | University College London Hospital |

## Contents

# 1 Overview of Life Study

## 1.1 Introduction

Life Study will be the UK's largest national birth cohort study and will gather data on more than 80,000 babies born in the UK, with recruitment beginning in 2014/15. The study has been developed by a cross-disciplinary research team, which includes leading biomedical and social scientists from across the UK. This document outlines the background, aims and methodology of Life Study and provides detailed information about the study protocol and first 'sweep' of data collection, which will follow babies from the prenatal period until the end of the first year of postnatal life. The protocol presented here was approved by the Research Ethics Committee in March 2014. Additional documents are available on the Life Study website at www.lifestudy.ac.uk.

The Life Study protocol was initially developed in response to the call specification for bids for leadership team for a new birth cohort study issued by ESRC and MRC in 2009.[1] This call specification (see Appendix 1) was informed by preceding reviews commissioned from Longview by the ESRC between 2006 and 2009.[2] Following international peer review and interviews by an international panel, ESRC awarded funding to the proposal from the leadership team led by Professor Dezateux. Funding was not released until mid-2011.

## 1.2 Overview and aims

Life Study is the first UK-wide study to start in pregnancy so will be able to collect data and consider factors before birth. The large size of the study will allow research into the impact of children's early environments on their future development. By following the early lives of babies born into today's society, Life Study will collect unique and rich information to answer important questions for children's health. Particular attention will be given to exploring ethnicity, household and family environment, and social and material disadvantage, and the interplay between biology and environment. The answers to a wide range of research questions and policy-relevant issues will help understand how to improve children's lives and those of future generations.

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[1] A Leadership Team for the 2012 Birth Cohort Study: Call Specification, April 2009. 2012_Cohort_Study_Leadership_Team_Specification_tcm6-31588.pdf reproduced at Appendix 1.

[2] (i) Strategic Review of Panel and Cohort Studies, 2006. (ii) Scientific Case for a New Cohort Study, 2007. (iii) Options for the Design of the 2012 Birth Cohort Study, 2009. These reports were undertaken by Longview and are available for download from http://www.slls.org.uk/#!longview-reports/c8a5.

Life Study will involve more than 80,000 UK babies and their families across England, Scotland, Wales and Northern Ireland. Women and their partners will be invited to take part during pregnancy, or soon after the birth, and they and their new baby (or babies) will be seen at Life Study Centres or in their own homes at least once during the first year after the birth. The study will observe the children and their families long-term, following the example set by previous long-term cohort studies. The design will allow Life Study to be compared with earlier UK birth cohorts while exploiting the opportunity to enrich the cohort with additional biological data as well as with contextual area-based information.

## 1.3 Rationale for Life Study

Life Study will be the fifth longitudinal birth cohort study in a series of world renowned UK studies which have followed the lives of children from birth to adult life. The first of these started post-war in 1946 (National Survey of Health and Development), and the most recent began at the turn of the 21st Century (Millennium Cohort Study). Since then, the demographics of the UK population has changed significantly, and Life Study will enable this increased diversity to be taken into account, as well as providing a wealth of insights into the health, development and life circumstances of a new generation of children.

## 1.4 Research themes

The aims of the study will be addressed through specific research questions around the following research themes:

- Inequalities, diversity and social mobility
- Early life antecedents of school readiness and later educational performance
- Developmental origins of health and illness in childhood
- Social, emotional and cognitive development: the interplay between infant and parent
- Neighbourhoods and environment: effects on child and family

Within each of these themes Life Study will explore cross-cutting issues, such as preterm birth or diverse families, and reflect contemporary UK population intergenerational influences on health and social outcomes. The cohort offers an opportunity to develop and test theoretical understanding of social and biological mechanisms operating through the life course, and to identify translational opportunities which might have early impact in relation to health and social policy.

Previous UK cohort studies have demonstrated that parental background is a major influence on children's development during pregnancy and infancy due to effects on maternal health, behaviour and parenting style as well as the social and material environment. A new scientific challenge is to capture the important inter- and intra-generational influences on child development in 21st century UK. New perspectives must be sensitive to social diversity and the pace of social change and capitalise on advances in life

sciences that help to clarify how biology and environment combine to influence development, health and well-being across the life course.

### 1.4.1 Continuity with previous cohorts

To investigate environmental and epigenetic influences on health, it is necessary to pool high quality data collaboratively with other cohorts and biobanks. To facilitate this, where appropriate, Life Study data collection protocols (including questionnaires) have been designed to be 'compatible' with their equivalents in other studies where appropriate.

### 1.4.2 Sample size

The proposed sample size for Life Study is much larger than previous longitudinal cohort studies and includes more than 60,000 pregnant women their babies and partners to be recruited through maternity units (Pregnancy Component) and 20,000 mothers, their babies and partners to be recruited after birth through national birth registrations (Birth Component).

The sample size for the Pregnancy Component will provide sufficient power to enable reliable detection of moderately strong aetiological effects (e.g. relative risk ≥1.5) associated with risk factors (environmental, psychosocial, genetic) that are moderately common (e.g. prevalence ≥ 10%) on outcomes that are other than rare (e.g. prevalence ≥0.5%). The sample size of 20,000 births for the national probability component is based on a detailed technical report on sampling for the Millennium Cohort Study (MCS)[3], and recommendations of the Longview Report[4]. A sample size of 20,000 maintains continuity with the Millennium Cohort Study and offers similar statistical power. The data from the Pregnancy and Birth Components will be integrated into a single dataset. Full details of the sample size calculations are presented in Appendix 3

## 1.5 Participants

The focus of this first funded phase of Life Study is the child in pre- and postnatal life. Initially, pregnant women in up to four urban areas of the UK will be invited to attend a Life Study Centre in the last five months of their pregnancy. At this visit, they will be asked to consent to their own participation in the study. When they attend the Life Study Centre on a second occasion when their baby is six months old, mothers (or the child's legal guardian)

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[3] The Millennium Cohort: Technical Report on Sampling 4th edition July 2007 edited by Ian Plewis; Centre for Longitudinal Studies ISBN 1 898453 62 4
http://www.cls.ioe.ac.uk/studies.asp?section=00010002000100050004

[4] (iii) Options for the Design of the 2012 Birth Cohort Study, 2009 available for download from http://www.slls.org.uk/#!longview-reports/c8a5.

will give consent to their baby's long-term involvement in the study. Children will have the opportunity to provide their own consent to continuing participation, as they grow older.

The mother's partner will also be invited to take part in Life Study. In most cases, this will be the biological father of the child (defined by the mother), however, where relevant, same-sex partners and non-biological parents or carers will also be encouraged to join. Information collected from non-biological parents or carers will enable examination of genetic and non-genetic intergenerational factors influencing child outcomes. The wider family of the child may eventually be invited to contribute data to Life Study but no contacts are envisaged in this first stage of Life Study.

## 1.6 Timeframe

The preparatory phase and pilot phases of Life Study were completed in December 2013. From January 2014, Life Study moved into its initial main phase which is referred to as Phase 1. Recruitment to Phase 1 will commence in late 2014 and will continue until mid-2016 when experience will be evaluated and plans for recruitment in Phase 2, currently anticipated to run until 2018, will be finalised. Currently it is anticipated that two centres will open in 2014 and the remaining two in 2016. Phase 1 will continue until October 2017 to allow all follow up visits until 12 months of age to be completed.

## 1.7 Funding

**Core funding:** Life Study is funded through the UK Government Department of Business Innovation and Skills (BIS) Large Facilities Capital Fund (LFCF), the Economic and Social Research Council (ESRC), Medical Research Council (MRC) and University College London (UCL). Life Study forms part of the Birth Cohort Facilities (BCF) Project. Life Study is subject to the Office of Government Commerce (OGC) Gateway Review Process and Gateway Reviews 4a and 4b occur prior to Phase 1 and Phase 2 respectively.

**Enhancement funding:** The Life Study Infection and Immunity Enhancement is being funded by a Wellcome Trust Strategic Award to UCL (Grant ref: WT101169AIA). Funding was also awarded by the Nuffield Foundation and the ESRC in March 2015 for development work and, subsequently, for an enhancement to Life Study to augment recruitment of non-resident fathers and resident fathers/partners (Nuffield Foundation grants ref: CPF/41196 and KID42046).

**NIHR CRN Portfolio:** Life Study is registered on the National Institute for Health Research (NIHR) Clinical Research Network (CRN) portfolio (ref: UKCRN ID 15560; LCRN CSP 109744). This provides access to support for NHS Trusts supporting the recruitment of mothers in pregnancy.

## 1.8 Research Ethics and Governance Approvals

Life Study has undergone full ethical review by the Health Research Authority (HRA) appointed London-City & East Research Ethics Committee (REC). Members of the REC approved Life Study on 22nd January 2013 (ref: 12/LO/1492) with subsequent amendments submitted to reflect the evolving protocol over the preparatory, pilot and innovation (Phase 1) phases for the Pregnancy and Birth Components. Approval has also been sought successfully from the HRA Confidentiality Advisory Group (CAG) under Section 251 (NHS Act 2006) for the proposed initial contact and recruitment methods (ref: ECC 5-05(b)/2012).

Life Study has been registered under the Data Protection Act 1998 as a UCL study (ref: Z6364106/2012/08/14) and the Information Commissioner's Office (ICO) was provided with details of Life Study in March 2013.

## 1.9 Organisational structures

### 1.9.1 The Life Study Scientific Director and Team

The Scientific Director of Life Study, Professor Carol Dezateux, is also the Life Study Principal Investigator (PI). She is based at UCL Institute of Child Health and is responsible for overall delivery of the project and overall scientific direction of the protocol. The Life Study team is based at the UCL Institute of Child Health and includes relevant expertise in clinical research, business operations, project management, information systems, communications and public engagement. The Life Study Executive meets weekly and comprises the Scientific Director; the Deputy and Associate Directors - Professors Elias and Brocklehurst respectively; the Chief Operating Officer Anne Carey, the Chief Scientific Officer Dr Debbie Colson; and the Life Study Finance Officer Jack Foster.

### 1.9.2 Governance structure and Committees

The Life Study committees, their roles and responsibilities are outlined below (see also Figure 1).

**Corporate Board:** Responsible for strategic decisions and accountable for funding.

**Management Board:** All funding bodies are represented at a senior level with decision-making authority.

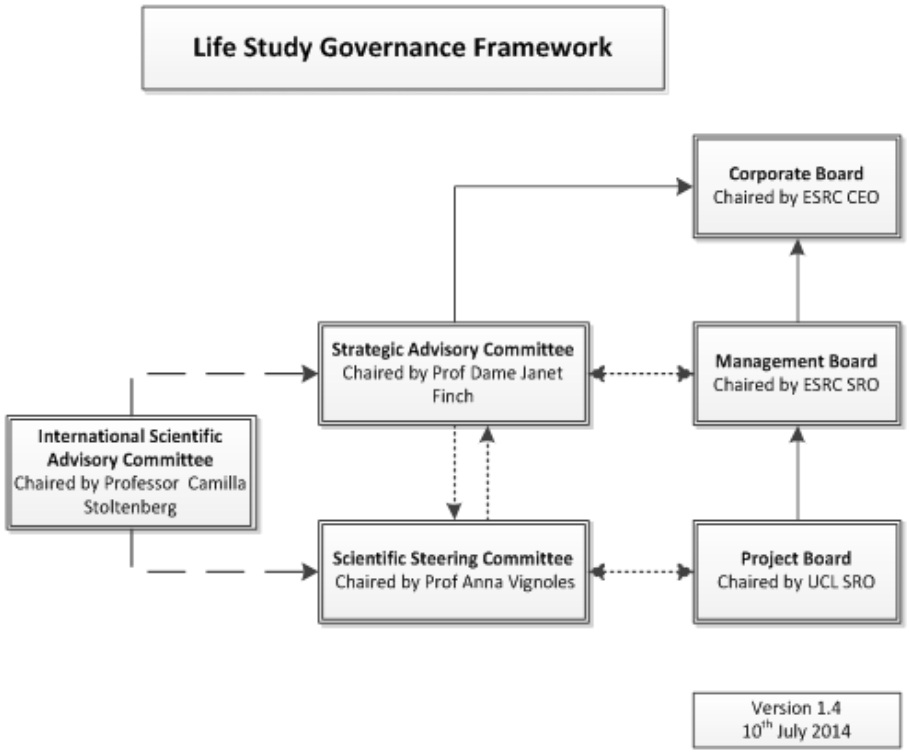
**Project Board:** Led from UCL and including membership from the Population Sciences Faculty, and UCL Finance, Procurement, IT, Human Resources and Facilities divisions; accountable for the project with the authority to direct the project within the remit set by Management Board

**Life Study Strategic Advisory Committee (LSSAC):** Provides independent assurance to the Management and Corporate Boards; Advises and challenges on strategic development and delivery.

**Scientific Steering Committee (SSC):** Provides expert advice on scientific, strategic, operational and related issues; Agrees the overall strategic and scientific direction and objectives of the Project; Advises on strategy and policy development. Subgroups of the SSC have specific remits, such as managing applications for 'enhancements' to the scientific protocol; these will normally be externally funded.

**International Scientific Advisory Committee (ISAC):** Acts as a scientific and strategic advisory committee; Advises on the scope of the scientific objectives and development of the resource to maximise its potential impact. Provides advice to the SSC and LSSAC.

Figure 1: Life Study governance structures for the main phase (2014)




## 1.10 Contacting Life Study

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# 2 Life Study Scientific Protocol

## 2.1 Study Design and sample size

Life Study has been designed to achieve scale (numbers of participants) and depth (nature and extent of the information to be collected), thus providing data to inform important research areas relating to early childhood development. Life Study has an innovative design comprising two samples – a clustered Pregnancy Component and a nationally representative Birth Component. See Appendix 2 for a summary Flow Diagram of the Study design.

### 2.1.1 Pregnancy Component

More than 60,000 pregnant women will be recruited through maternity units, with over-representation of women from ethnic minority groups relative to the UK birth population as a whole and reflecting the population in which the Life Study will be located. The principles underlying the selection of the maternity units are outlined in Appendix 4.

Mothers and partners will be invited to attend a Life Study Centre near their maternity unit on one occasion from the 20th week of pregnancy onwards, and again when their baby is six months and 12 months old.

### 2.1.2 Birth Component

The Birth Component will be a UK-wide sample of 20,000 births recruited using a clustered survey sampling design based on birth registrations and including approximately 16,000 participants in England with the remainder drawn from Wales, Northern Ireland and Scotland.

The Birth Component sample will allow inferences to be made from the data in the Pregnancy Component to the national population, facilitating comparability with earlier cohorts, and will allow researchers to explore possible biases in the Pregnancy Component sample when studying relationships between variables.

### 2.1.3 An integrated dataset

Integrating the Birth Component and Pregnancy Component will allow inferences to the national population, as well as exploration of possible biases in the Pregnancy Component sample. This requires that the two samples are recruited from births occurring within the same time period. The potential for secular trends also makes it essential that information from the Pregnancy Component sample can be anchored in information derived from a Birth Component sample that is contemporaneous.

The recruitment period is estimated to be four years, thus the cohort will consist of children with a 3-4 year difference in their ages. This will be a very valuable resource to study childhood development and links with gene/environment expression. A spread of ages at follow-up can also be an advantage at certain transitions in the life course for quantitative traits, e.g. the analysis of growth patterns in infancy and early childhood and at puberty in adolescence.

The Life Study design enables research findings to be placed within the context of a nationally representative population of very young children and will lay the foundation for a continuing longitudinal study of children born between 2014 and 2018. This will position the Life Study firmly within the UK's powerful series of major birth cohort studies as the largest and most detailed birth cohort study ever conducted in the UK. The Life Study will comprise a rich resource of longitudinal data and biological samples across all domains of relevance to the early years that will be used by a wide range of researchers to address research and policy questions from a life course perspective.

### 2.1.4 Sample size

Information collected from participants will contribute to a single integrated dataset of more than 80,000 mothers, their babies and partners, more than 200,000 participants in total. This sample size provides adequate statistical power to support robust analyses of the interplay between biology and environment. Details of the sample size estimates, proposed dataset integration and methodology for developing statistical weights are provided in Appendix 3.

## 2.2 Development of the scientific protocol

The draft scientific protocol was developed with input from clinicians, social and biomedical scientists and other relevant experts. The data collection instruments and measures were designed to reflect the scientific vision and key research themes, capitalise on the unique opportunities of this stage in the infant life course and to enable a wide range of policy issues relevant to children and health to be explored. The Scientific Steering Committee (SSC) maintained an overview of the process and was responsible for the final prioritisation of measures and instruments.

**Scientific Research Investigator Network Meeting:** In November 2011, a two day meeting was attended by 40 members of the SRIN, which includes Life Study co-investigators, as well as additional experts from the social and biomedical sciences. Attendees identified and discussed the development of the protocol.

**Review of other birth cohorts and longitudinal studies**: The Life Study team reviewed previous longitudinal studies to inform protocol development, including identifying relevant instruments and opportunities for cross-cohort comparisons.

**Scientific Working Groups (SWGs):** Six SWGs were established and co-chaired by social and biomedical scientists. SWG members identified and prioritised data collection instruments that could be included. A number of subgroups were also established, for example to consider mental health, and individual experts were also consulted.

**Scientific Protocol Development Group (SPDG):** The SWG co-chairs together formed the SPDG which coordinated the integration of recommendations from the individual SWGs into a single draft protocol.

**Prioritisation of measures for inclusion:** An initial prioritisation of the measures and instruments was undertaken by the SPDG in June 2012 and this was followed by a final prioritisation by the SSC in July 2012. External facilitators (Centre for Facilitation, CFF) assisted the prioritisation process.

**Public consultation on the scientific protocol**: Public and expert consultation on the draft scientific protocol was achieved through a consultative conference (held on 17th July 2012; 60-70 attendees; external facilitation by the Centre for Facilitation) and an independently conducted web-survey (TwoCan Associates, August 2012).

### 2.2.1 Criteria for including instruments and measures

The selection and prioritisation of data collection instruments was driven by clear criteria, including:

- their potential scientific contribution to understanding the interplay between biology and the environment in shaping children's (unequal) health and future wellbeing;
- their reliability and public acceptability;
- the opportunities for harmonisation with other national and international studies, including UK birth cohorts, to facilitate inter-study comparability; and
- the obligation to minimise the burden on participants.

### 2.2.2 Excluded instruments and questions

Several measures were proposed but excluded after consultation. Criteria for excluding measures comprised measures that:

- can be found elsewhere, for example the handheld maternity record, hospital obstetric notes or baby's 'Red Book';
- were regarded as potentially sensitive and more appropriate to a later visit when a participant has established greater commitment to the study, such as measures to identify ADHD and autism traits in the mother.

## 2.3 Data collection

### 2.3.1 Pregnancy Component

**Pregnancy visit:** Women, and their partners if they attend, will formally consent to take part, complete a questionnaire, be measured (height, weight and body fat), have eye tests, and provide blood and urine samples.

**Birth:** Biological samples, for example saliva, urine, faeces and placenta will be obtained shortly around the time of birth from mothers who have previously consented to collection from them and their newborn babies. Any blood samples left over from the antenatal booking or screening tests or the baby's newborn bloodspot screening (heel prick) test will also be collected and stored with the mother's permission.

**Six and 12-month visits:** Mothers (or parents) will complete questionnaires (including pre-or post-visit questionnaires) and their baby will have detailed measures of body size and neurodevelopment, including observations of maternal-infant interaction and eye tests. Samples of urine, faeces, saliva and oral fluid will be obtained from babies at 6 months (using non-invasive methods.), and again at 12 months. At the 12 month visit, samples of blood and urine will be requested from mothers.

Additional information will be sought from the handheld maternity record that women carry throughout pregnancy, the mother's hospital obstetric notes relating to pregnancy and birth, and from babies' personal child health record (the PCHR or 'Red Book').

### 2.3.2 Birth Component

**Six and 12 month visits**: Birth Component participants (mothers, partner/fathers and babies) will be visited at home when the baby is six months old. The home interview will collect similar information as for the Pregnancy Component, but biological samples and physical measurements will not be collected. Information about the pregnancy and delivery will be collected retrospectively and a pre-visit questionnaire may be used. A further assessment using postal/web/telephone data collection methods will take place when the baby is 12 months of age.

## 2.4 Recruitment

The proposed pathways for recruitment in the main phase are outlined here.

### 2.4.1 Pregnancy Component

All pregnant women who attend the 18-22 week fetal anomaly scan (described below as the 20 week scan) within the participating maternity units will be invited to take part in Life Study. Women who book to deliver within a participating maternity unit will receive a flyer about Life Study at the time of their routine booking appointment or scan (around 8-16 weeks of pregnancy and described below as booking). Women will be informed that they can notify their maternity unit staff if they do not wish to speak to research staff. Posters will be displayed in the maternity unit and will also highlight that the unit is participating in the study.

**Recruitment by research midwives (integrated NHS pathway):** Where possible the participating maternity unit will employ practising midwives as part of the clinical care team who are also seconded to Life Study part-time. At the 20 week scan appointment, these midwives can provide pregnant women with information about Life Study and an invitation to participate. This model will be implemented and evaluated in the first Life Study Centres (Barking, Havering and Redbridge University Hospitals Trust, BHRUT and the University Hospitals of Leicester NHS Trust). Implementation in maternity units associated with future Life Study Centres will depend on local agreements.

**Recruitment by postal contact:** Should the integrated NHS pathway not be possible in the remaining Life Study Centres and maternity units, women will be informed in a flyer that they will be sent an invitation to participate in Life Study, unless they indicate to the maternity staff that they wish to dissent from receiving any invitation. If women do not indicate that they wish to dissent, their contact details will be passed by the maternity unit to the central 'mailing house'. The mailing house will be the Data Linkage and Extract Service (DLES), formerly called the Medical Research Information Service, which is based at the NHS Health and Social Care Information Centre (HSCIC). In line with approval obtained previously for Life Study[5], DLES can act as a trusted third party (TTP) for personal information that is held prior to individual consent, and would send an invitation to participate in Life Study on behalf of the research team along with a letter of support from the local responsible obstetrician. Information about non-responders would be collected by DLES to evaluate and characterise response bias. This process is similar to that proposed for contact with the Birth Component as described below.

See Appendix 5 for an outline of the recruitment pathway.

[5] Life Study has obtained approval from the Health Research Authority Confidentiality Advisory Group (CAG) under Section 251 of the NHS Act 2006, for a mailing house to be operated by DLES, which operates to IG Toolkit and ISO27001 standards for information systems security.

### 2.4.2 Birth Component

**Recruitment by postal contact**: Initial identification of babies eligible to be invited to participate in the Birth Component in Life Study will be through random sampling of new birth registrations across the UK. New births must be registered within six weeks (42 days) of birth. Staff at the Office for National Statistics (ONS) will randomly sample births in England and Wales (using a sampling frame defined by Life Study statisticians). A cross-check against mother and baby's data would be undertaken prior to mailout to ensure letters are not sent to households in which either the mother or baby has died.

ONS staff will send the first letter of invitation on behalf of Life Study to the randomly selected mothers in England and Wales, and up to three reminder letters to non-responders at intervals of 2-3 weeks. ONS have previously sent mailouts on behalf of researchers.

A similar approach to recruitment will be used in Scotland and Northern Ireland through the respective birth registration systems (National Records Scotland [NRS] and Northern Ireland Statistics and Research Agency [NISRA]). Appropriate approvals will be sought.

See Appendix 5 for an outline of the recruitment pathway.

## 2.5 Consent

**Pregnancy Component:** Consent to take part in Life Study will be sought from mothers and partners at the Life Study Centre at the start of the pregnancy visit. Consent for biological samples to be taken from mother and baby at birth will also be taken at this visit to avoid consent being required during labour.

**Consent for the unborn baby** to participate will initially be taken at the pregnancy visit so that the birth outcome and baby can be followed up to the second visit. At the second visit, when babies are around six months old, the mother or parent will reconfirm consent to the baby's participation in Life Study.

**Birth Component:** Consent to take part in Life Study will be sought from and for all participants at the home visit.

Table 1: Timing of consent in the Pregnancy Component

| Timing of request | Consent from | Consent for |
|---|---|---|
| **Pregnancy visit** | Mother | First pregnancy visit; biological samples at all visits; routine record linkage; participation in Life Study; future contact. |
| | Father/Partner | First interview & visit; biological samples at the visit; routine record linkage; participation in Life Study; future contact. |
| **Unborn baby** | Mother (or parent/legal guardian) | Biological samples at birth; routine record linkage; participation up to six months of age. |
| **Six month old infant** | Mother (or parent/legal guardian) | Biological samples at 6 and 12 month visits; details of birth outcome; routine record linkage; participation in Life Study; future contact. |

### 2.5.1 Teenage mothers

Although a child under the age of 16 years is below the legal age to consent, they are often considered to have the capacity to consent to their own healthcare treatment and interventions. They are also frequently asked to provide assent to participation in health research, when a parent or legal guardian has consented on their behalf. As mothers in Life Study are being asked to consent to participation long-term in research not only for themselves but also for their babies, we have sought advice from legal experts and concluded that pregnant girls or mothers under the age of 16 years will not be recruited to Life Study. The basis for this decision is outlined in more detail in the Life Study Ethics, Information Governance and Access Framework (available from www.lifestudy.ac.uk).

### 2.5.2 Consent for the unborn baby

Before birth, the unborn baby is not considered a legal entity and taking parental consent to long-term participation in Life Study could be contested. However an important principle is that seeking consent for the baby to be involved in the study should not be sought at birth, as this is likely to be a time when mothers may not be in a position to appropriately consider and give informed consent. At the pregnancy visit, consent will therefore be sought from mothers to obtain biological samples from the baby at birth[6] and to undertake record

[6] In studies of emergency neonatal care it has often been considered acceptable to seek consent before birth as parents are often better able to consider the decision in their own time and thus make an informed decision.

linkage to health-related records from birth. Consent for the baby to participate long-term in Life Study, for record linkage to education records and for the collection, long-term retention and use of samples, will be sought from the mother during the visit when babies are aged six months.

## 2.6 Partners

The child's biological father, or the mother's partner, are of key importance to the child's early life development, through their genetic contribution and/or influence on the caring environment that the child experiences. Consideration has been given to the method of first contact with partners as they are often excluded from longitudinal cohort studies. In the Pregnancy Component, research midwives will approach partners who attend the antenatal clinic and scans to provide them with information about the study and invite them to participate. If partners do not attend, each woman will be given an information pack (containing a covering letter and participant information sheet) for her partner. Women will be allowed to choose to whom they give the 'partner's pack', this may be the child's biological father or another partner who will help care for the baby. They may choose not to pass on the pack at all. When they confirm their appointment, pregnant women will be asked if they are willing to provide the name and relevant contact details of the partner to whom they have passed the information pack.

Life Study also aims to collect partner's contact details, dates of birth and NHS numbers from women at the time of the first contact or visit, to allow partners to be invited individually in their own right to be participants in the study. This will be undertaken with the woman's permission and is considered unlikely to be disclosive as the partner's details are usually provided as next of kin on the maternity record, and fathers are often named on the official birth registration. However, Life Study will have a procedure for registering any complaints that may arise from a woman providing her partner's contact details and will address these appropriately.

Partners may also directly contact or 'register' online with Life Study to confirm their interest in participating and provide contact details so they may be contacted directly in future. The acceptability of this approach to fathers and partners will also be tested with potential participants early in the recruitment phase.

Partners/fathers may attend the Life Study Centre with the mother or at another convenient time. In the Birth Component, both the mother and her partner will be invited to be present at the home visit and every effort will be made to carry out interviews when both are present.

The Life Study pilot, as well as experience from other cohort studies, suggests that partners may be less responsive to the invitation to take part than mothers and are also likely to favour different modes of data collection, for example e.g. post, web- or text-based.

The Life Study Expert Advisory Group on Fathers and Partners was established to address the specific challenges and opportunities of including fathers/partners as participants, and to advise on a proposal to the Nuffield Foundation to augment the recruitment and retention of resident and non-resident fathers/partners in the Life Study in order to address two major aims:

- Describe trajectories of resident and non-resident fatherhood/partnering from pregnancy and in early life;
- Examine how a father/partner's anticipated involvement in their child's life as reported during pregnancy relates to their involvement after once the child is born.

The additional funding awarded in March 2015 by the Nuffield Foundation for this project will permit augmented recruitment of non-resident fathers/partners, with a particular emphasis on the Birth Component, and on resident and non-resident fathers/partners newly identified by mothers following the birth of the child in the Pregnancy Component (including after a change in partner). In addition, retention of fathers/partners will be improved by offering at least one further contact (including different contact types, such as web- and telephone-based interviews) following recruitment and before the child's first birthday and requesting consent to record linkage in those who have not previously provided this.

## 2.7 Pregnancy Component: Life Study Centre Visit

### 2.7.1 Invitation and appointment scheduling

At the 20 week scan, pregnant women will be approached by the research midwife and given an invitation, participant information sheet and, if willing, a provisional appointment to attend their local Life Study Centre. Women may delay making an appointment and will be given full details of how to make or cancel an appointment. A double appointment for the woman and her partner will be arranged if both wish to participate and attend together.

Contact to confirm an appointment will be through phoning (free of charge) or returning a reply paid card to the Life Study Centre which will then schedule appointments and ensure efficient use of the Life Study Centre. Text and web-based appointment confirmation or scheduling option will also be activated if feasible.

### 2.7.2 Estimated Recruitment

Duration of recruitment has been estimated using an estimated response rate of 50% in the Pregnancy Component. This estimate is based on other birth cohorts; MoBA recruited 35% of mothers approached in pregnancy, Born in Bradford 70% and ALSPAC an estimated 70%.

The Millennium Cohort Study (MCS), which contacted mothers after birth, achieved a response rate over 70%. Life Study recruitment will be monitored closely during the main fieldwork and the Study has been phased to enable recruitment methods in pregnancy to be tested and refined before opening the remaining Centres. Life Study will also develop a careful programme of local community engagement to encourage participation, solicit local views on the study (e.g. identifying local issues or concerns) and to inform local communities about the study. The Birth Component recruitment and retention will be tested and refined in a longitudinal pilot study.

### 2.7.3 Pilot of the Pregnancy Component visits

A pilot of the Life Study visit for the Pregnancy Component was undertaken from September 2013 to November 2013 (approved under Life Study substantive amendment 2.0, dated 10th September 2013). Life Study commissioned a fieldwork agency (NatCen Social Research) to undertake the pilot evaluation. The objectives of the pilot were to validate, test and operationalise the scientific protocol, including the questionnaires, interview and assessment schedules, instrumentation and standard operating procedures (SOPs).

All four participant types (pregnant women, partners, 6 and 12 month old babies with their mothers) were included in the pilot but each participant was seen only once and there was no longitudinal follow-up or record linkage. The only biosamples taken were saliva and urine from infants to test the methods for collection. Mothers of 12 month old infants also wore an accelerometer over several days so that the instrumentation, feasibility of measurement and acceptability of these could be evaluated. The pilot recruited 41 participants, including 26 pregnant women, 6 male partners, 4 mothers with babies aged 4-8 months and 5 mothers with babies aged 10-14 months. A short report, highlighting potential lessons from the pilot for the final scientific protocol and main phase of Life Study, was provided to the SSC. The scientific protocol to be used in the main phase visits have been informed by results from the pilot feedback, which included the acceptability of different measures to participants.

Life Study will utilise a Day 100 plan, in which the first 100 operating days of the first Life Study Centre will also be a period of phased implementation and focused evaluation of the study instruments and procedures to confirm these are acceptable to participants and that Life Study research data are being collected to the required quality and standard.

### 2.7.4 Visit duration

Data collection has been based on an average Life Study Centre visit of around 2 hours, including introduction and consent (15-20 minutes), questionnaires, interviews and physical measures and biological sampling (90 minutes), and a closing discussion with participants (10-15 minutes). The effect of fixed or flexible ordering of measurement stations and the

timings for each assessment were tested in the pilot and, where appropriate, compared with the original estimates. The inclusion, exclusion and revision of different questions were reviewed and final changes agreed by the SSC.

### 2.7.5 Staff training

Appropriately skilled staff will be trained to assess participants attending the Life Study Centres. Staff will have previous experience in health care, such as midwives, nurses, health care assistants and phlebotomists, and they will be employed jointly between the NHS and Life Study. They will be fully trained in their defined role for Life Study, for example in the pilot, interviewers with experience of undertaking home interviews in previous cohort studies were trained to undertake the physical measurements, while nurses undertook the biological sampling.

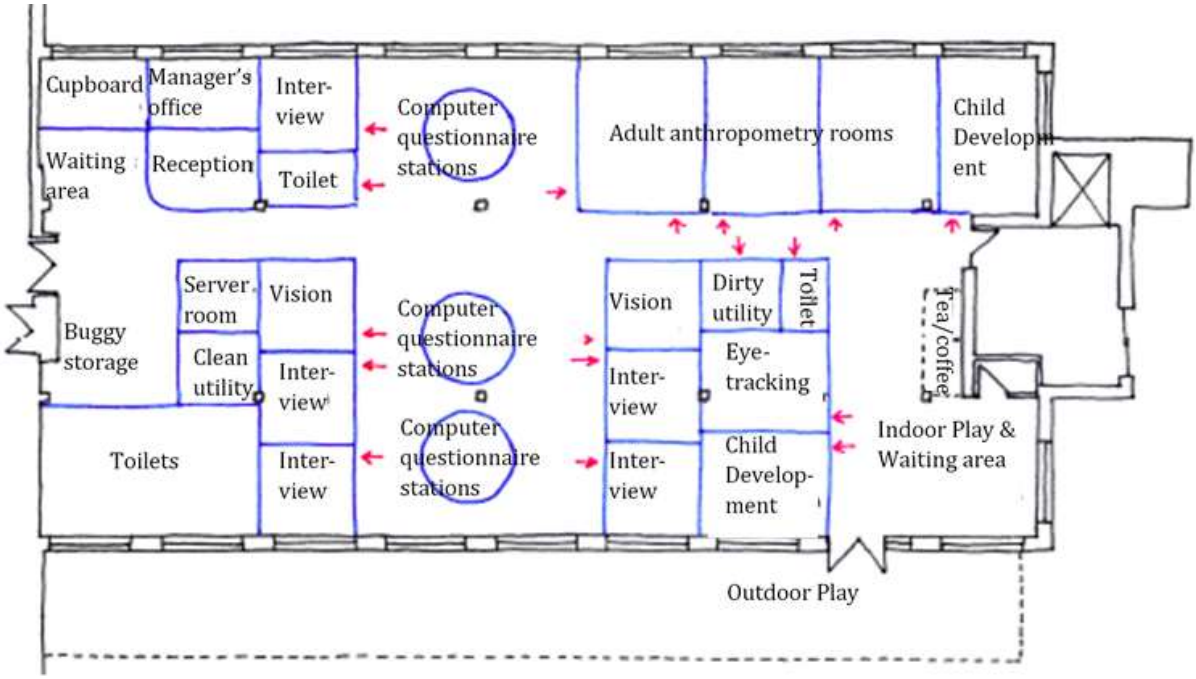
### 2.7.6 Assessment stations

Participants will move through a series of dedicated stations, including:

- Interview
- Self-complete computer questionnaire
- Adult and infant anthropometry
- Child development testing
- Vision testing
- Biological sampling.

A proposed layout for these 'stations' in the Life Study Centres is provided in Figure 2. The Centres will also include play and breastfeeding facilities.

Figure 2: Proposed layout for Life Study Centres indicating different stations to be included*




*the layout omits the blood sampling room which may be located within the adjacent antenatal clinic or in the Centre depending on local arrangements.

### 2.7.7 Accessibility

Barriers to participation will be minimised for all participants. Participants who confirm an appointment will be asked about any specific requirements for language and access.

**Language and communication:** Through liaison with maternity units, the main languages used by local mothers will be identified and written information translated into the relevant languages. Staff recruitment in Life Study Centres will take account of local language needs and interpreting facilities will be procured as required to support participants in languages other than English, including sign language. Questionnaires will be provided in an aural format for women who have visual or literacy difficulties. The participation of women with hearing difficulties will be supported through written materials or signing.

**Mobility issues:** Life Study Centres will be selected to be suitable for a healthcare purpose and internally designed to be easily accessible to participants using wheelchairs or mobility devices, as well as for prams, buggies and pushchairs.

**Transport:** The location of a centre will take account of transport links for women who attend the local maternity unit.

### 2.7.8 Reimbursement of travel expenses

Participants attending the Life Study Centre will be offered reimbursement of their travel expenses. In recognition that women may wish to have someone accompany them to help

out with children or look after them if they feel unwell, one accompanying individual will also be eligible for reimbursement of travel. At the end of each visit, expenses will be provided or an explanation given of how to claim these.

#### 2.7.9 Life Study Standard Operating Procedures and Policies

Life Study Standard Operating Procedures for each stage of the visits for the Pregnancy Component were developed for the pilot and staff training was undertaken to support implementation of these. Feedback from the pilot included evaluation of the SOPs; some amendments have been made and they are now appropriate for use in the main phase.

The Standard Operating Procedures are available as separate reports for download on the 'Resources' page of the Life Study website www.lifestudy.ac.uk.

Additional policies were also put in place for both the pregnancy and birth components, reflecting policies of the local NHS Trusts, the Fieldwork Agency or the Biorepository Provider responsible for employing and training staff delivering the Study. These included and which they were trained, including those relevant to Information Governance and Data Protection, Serious Adverse Events, Incident Management, Safeguarding, Health and Safety and Complaints Procedures.

##### 2.7.9.1 Health or safeguarding concerns

As the Pregnancy Component is being carried out in NHS facilities and is recruiting NHS patients, should Centre staff have any clinical concerns about the results of any assessments during the visits, they will notify the Centre Manager in accordance with the written Life Study policy. Concerns will be discussed with the local Trust or area Safeguarding Team and advice sought. Life Study has developed and implemented a Safeguarding Policy and provided Level 1 Safeguarding training for staff involved in the Life Study pilot. This policy was adapted to meet any local requirements and implemented in all Life Study Centres.

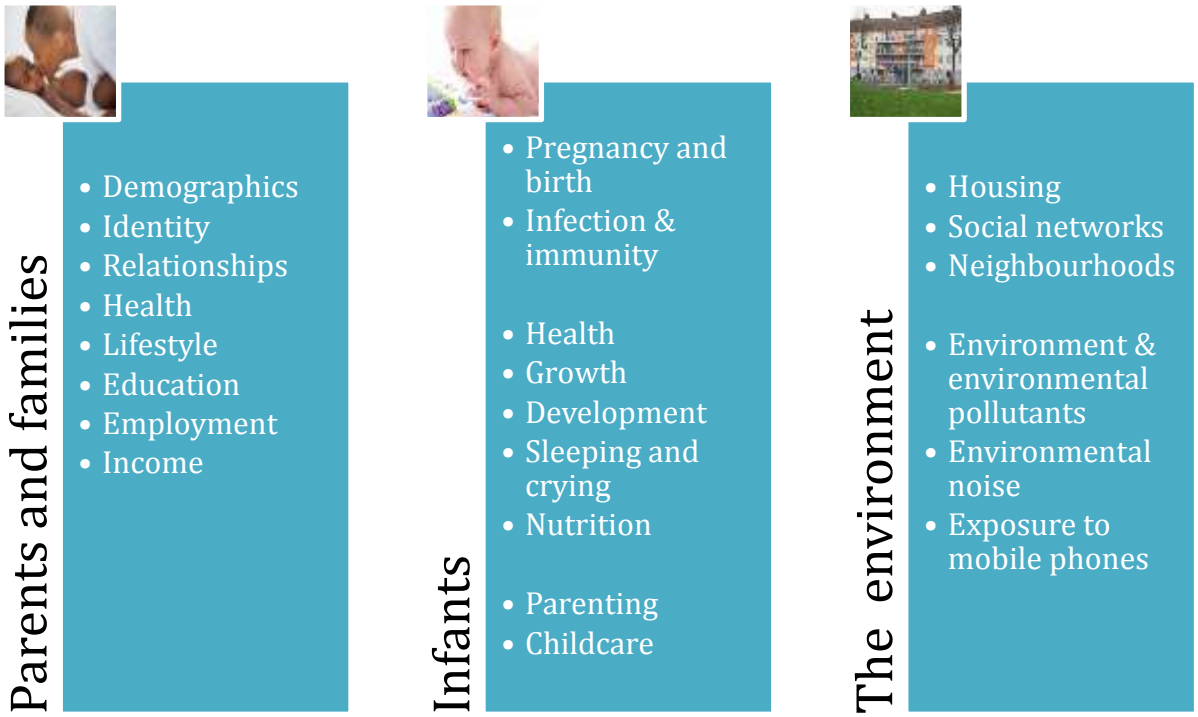
## 2.8 Life Study Questionnaires and Measurements

### 2.8.1 Questionnaires and interviews

#### 2.8.1.1 Topic Groupings and High-level Topic Areas

The information that will be collected through self-complete and interviewer-led questionnaires can be divided into three broad topic groupings and a set of higher-level topics are contained within each of these (Figure 3)

Figure 3: High-level topic areas




Topics and question modules for the main phase questionnaire and interview schedules were agreed by the SSC (see Appendix 6).The Questionnaires for the pregnancy and birth components for all currently planned stages of Life Study are available from the 'Resources' page of the Life Study website.[7]

### 2.8.2 Physical Measurements

The physical measures to be performed at the assessment centre include:

#### 2.8.2.1 Anthropometry

This term refers to the measurement of height, weight, body size and composition, and changes in these over time. Women will be measured in pregnancy and at 12 months, partners at the first visit and babies at both the 6 and 12 month visits. The measures undertaken in adults will include sitting and standing height, bioimpedance[8] (body composition), weight, triceps and subscapular skinfold thickness (using Holtain calipers), and waist circumference. In babies, the measures will include length and weight, and

[7] www.lifestudy.ac.uk

[8] Bioimpedance has been previously used in pregnant women and is considered safe for mother or baby. The only exclusions are for those wearing pacemakers or with any prosthesis.

subscapular skinfold thickness (using Holtain calipers), mid-upper arm circumference and head circumference.

#### 2.8.2.2 Vision

The vision tests will be undertaken in adults (at the pregnancy visit) and infants (when aged 12 months). They include plusoptiX screening for malalignment of the eyes (squint), a Frisby stereovision assessment (as a test of neurocognitive function), and assessment of refractive error by measuring the glasses prescription (using a focimeter or transcription of the prescription). A digital photograph of the eyes will be taken if the plusoptiX screening tool cannot register both eyes.

#### 2.8.2.3 Child Development

**Eye-tracking (Gap Task):** The baby's visual attention will be assessed using the Tobii Eye Tracker at 6 and 12 months of age. Cameras will record the baby's responses to a series of images on a screen.

**Child Development Assessments:** The baby's development will be assessed during a series of tasks performed with the mother (or caring adult) at the 6 and 12 month visits. These activities will be recorded using a digital camera and scored later against a scoring standard. The activities at 6 months will include mother-baby interaction. At 12 months, the tasks include restraint in a high chair, and a joint attention task.

The Standard Operating Procedures for the anthropometry, vision and child development assessments for all currently planned stages of Life Study are available from the 'Resources' page of the Life Study website.[9]

Table 2: Physical measures assessed in the pilot

| | Pregnancy visit | | 6 month visit | | 12 month visit | |
|---|---|---|---|---|---|---|
| | Mother | Partner | Mother | Baby | Mother | Baby |
| ANTHROPOMETRY | | | | | | |
| Weight (Infant and Adult) | ✓ | ✓ | | ✓ | ✓ | ✓ |
| Adult Bioimpedance (BIA) | ✓ | ✓ | | | ✓ | |
| Adult height | ✓ | ✓ | | | | |
| Infant length | | | | ✓ | | ✓ |
| Adult sitting height | ✓ | | | | | |

[9] www.lifestudy.ac.uk

| | | | | | | |
|---|---|---|---|---|---|---|
| Adult waist circumference | | ✓ | | | ✓ | |
| Skinfold thickness | ✓ | ✓ | | ✓ | ✓ | ✓ |
| Infant head girth | | | | ✓ | | ✓ |
| VISION | | | | | | |
| Eye examination (plusoptiX) | ✓ | ✓ | | | | ✓ |
| Photograph of eyes | ✓ | ✓ | | | | ✓ |
| Stereovision (Frisby test) | ✓ | ✓ | | | | ✓ |
| CHILD OBSERVATIONS | | | | | | |
| Gap Task (eye-tracking) | | | | ✓ | | ✓ |
| Restraint in high chair | | | | | | ✓ |
| Mother-baby interaction | | | | ✓ | | |
| Joint attention | | | | | | ✓ |

## 2.9 Biological Samples (Pregnancy Component)

Biological samples will be collected, with consent, from Pregnancy Component participants only. At the Life Study Centre pregnancy and partner visits, blood, urine and saliva will be collected from the mothers and their partners. At the six and 12 month visits, urine and saliva will be collected from the babies. Samples will also be collected in hospitals at birth (see below).

The collection of biological samples (biosamples) will be minimally invasive to cause as little distress as possible. Blood sampling will only be undertaken from adults and no blood tests are to be carried out on the infants. Blood samples will be taken by staff trained in phlebotomy.

The newborn bloodspot (NBS) is routinely collected from all babies born in the UK at 5-8 days of age and used to screen for a range of disorders (further details of the screening programme are available at: http://newbornbloodspot.screening.nhs.uk/). Residual bloodspots, 'leftover' after newborn screening has been completed, are stored for research and will be retrieved by Life Study to provide a source of infant blood. Cord blood will also be taken at birth when this is possible.

### 2.9.1 Collection of biological samples at the Life Study Centre

**At their first visit to the Life Study Centre,** mothers and partners will be asked to provide blood, urine and saliva samples (see Table 2). A sample of 40-50ml of blood (about 3

tablespoons) will be taken from each participant.[10] Pregnant women will be prompted to bring their handheld maternity records to their first visit when consent will be sought for the collection of umbilical cord and other biological samples at birth (see Table 4).[11] The mother's consent for sample collection at birth will be recorded in her maternity record.

**At the 6 month visit:** when a mother attends with her baby, samples of urine, faeces, oral fluid and saliva from the baby (but not blood) will be obtained. No samples will be taken from the mother at this visit.

**At the 12 month visit:** mothers will be asked to provide an additional 40-50ml sample of blood, and a urine sample. Urine, stool (faecal sample), saliva and oral fluid samples will be sought from the baby.

The collection of the biosamples listed in Table 3 was evaluated in infants in the pilot (Sept to Nov 2013, performed by NatCen Social Research on behalf of Life Study). A report of the Standard Operating Procedures for Biosamples is available from the 'Resources' page of the Life Study website.[12]

Table 3: Biosamples collected from infants in the pilot

| Biosamples to be collected from Infants | 6 month visit | 12 month visit |
|---|---|---|
| Infant urine – using cotton wool balls | ✓ | ✓ |
| Infant saliva – using Oragene 'sponge on stick' kits | ✓ | ✓ |

### 2.9.2 Collection of biological samples at birth

Women recruited to the Pregnancy Component will be booked to deliver in one of the participating maternity units and the collection of samples around the time of birth will be facilitated by this design. Consent to collection of samples at birth will be taken at the Life Study Centre pregnancy visit and recorded clearly in the women's maternity notes along with detailed instructions for the collection of samples. Midwives in collaborating maternity units will be briefed and trained to collect samples.

[10] This sample was acceptable to participants in the UK Biobank study and is not greater than the sample taken from pregnant women attending the maternity unit at the time of booking.
[11] These samples are viewed legally as 'maternal waste' products, therefore maternal consent can be given before birth.
[12] www.lifestudy.ac.uk

Additional funding has been secured from the Wellcome Trust for an enhancement, which will allow additional samples to be collected around the time of birth to specifically investigate aspects of infection and immunity and the impact on later outcomes (including the role of the microbiome, PI: Professor P Brocklehurst, UCL Institute for Women's Health and Associate Director of Life Study). A pilot to evaluate the feasibility of sample collection at birth and any sample processing requirements prior to long-term storage was carried out at UCLH in February 2014 (REC substantive amendment 3.0, approved 2nd Jan 2014). The results informed the final list of samples to be collected at birth in the main phase of Life Study. Table 4 summarises the biological samples to be requested and collected during visits and at birth.

### 2.9.3 Processing and storage of biosamples

The principles underlying the methods chosen for sample collection and processing are to:

- Collect, process and store samples to serve as wide a range of scientific investigation as can be anticipated
- Reject material for collection where a single measure will be too variable (e.g. salivary cortisol) or the molecule of interest can be measured in samples already included in the study
- Avoid processing approaches that preclude some future analyses
- Centralise and standardise processing methodology to ensure consistency and reproducibility, and reduce cost
- Provide a broad, secure and consistent dataset on each participant sample through the use of automated, highly validated assays.

Storage and processing of samples will take into account the assays that are anticipated to be the most likely to be undertaken in future, for example whole genome sequencing (see Table 5). In order to maintain biological sample quality and minimise degradation, samples will be stored in the most appropriate conditions feasible, and freeze/thaw cycles will be limited where possible. This is likely to include long-term storage in a biobank archive at ultra-low temperatures to ensure long-term stability and integrity, e.g. -80°C. In selecting the most appropriate mode of storage for biological samples, the anticipated demand for samples may be balanced against the costs of storage and the costs and expected error rates of sample retrieval. Back-up samples will be stored securely in a second geographical location.

Table 4: Sample types to be obtained by setting, participant and sample type

| Setting | Participant and timing | Protocol type | Sample type |
|---|---|---|---|
| **Life Study Centre Visit** | | | |
| | Mother in pregnancy | | |
| | | Core | Blood, Urine |

| | | | |
|---|---|---|---|
| | Father/partner in pregnancy | | |
| | | Core | Blood, Saliva, Urine Blood/Saliva[1] Urine |
| | Baby at 6 months | | |
| | | Core | Urine, Saliva[1] |
| | | Enhancement | Oral fluid, Faeces |
| | Baby at 12 months (Phase 1 only) | | |
| | | Core | Urine |
| | | Enhancement | Oral fluid, Faeces |
| | Mother at 12 months (Phase 1 only) | | |
| | | Core | Blood, Urine |
| **NHS setting** | | | |
| | Baby at birth | | |
| | | Core | Placenta, Placental Membranes, Umbilical cord |
| | | Enhancement | Cord blood, nasopharyngeal swab, Urine, Meconium/faeces, (including faecal and urine samples collected during the first two weeks of life by mother, midwife or health visitor and posted to Life Study) |
| | Mother at delivery | | |
| | | Enhancement | Vaginal swab, Urine, Faeces |
| | NHS left over samples | Core | Maternal antenatal screening serum, newborn screening dried blood spot |

(1) Saliva will only be collected from multiple births (twins etc) and babies for whom no placenta was collected, to provide a source of DNA.

Table 5: Indicative analytes (i.e. samples stored for these purposes)

| Indicative analytes |
|---|
| **Genome and Epigenome** |
| • Whole genome/exome sequence: blood, placenta |
| • Epigenetics – eg methylation: blood, placenta, saliva |
| • *RNA, transcriptomics(1) |
| |
| **'Infectome' and Immunity** |
| • Microbiome – vaginal and faecal mother, infant faecal |
| • Infections – e.g. CMV, EBV, VZV antibodies and/or DNA: cord blood, maternal blood, oral fluid |
| • Immunology: immunophenotype: cord blood, parental blood, placenta |
| • C reactive protein |
| |
| **Metabolome including Endocrine and Biochemistry** |
| • metabolomics: urine, placenta, blood |
| • Thyroid, parathyroid: maternal and infant blood |
| • Plasma Calcium Phosphate and Alkaline Phosphatase - |
| • Lipids |
| • HbA1C |
| |
| **Exposome: Micronutrients and vitamins** |
| • Folate: maternal, infant blood |
| • Iodine: maternal and infant urine |
| • Vitamin D: Serum 25-hydroxyvitamin D and 1,25-hydroxyvitamin D3: maternal and infant blood |
| |
| **Exposome: Pollutants** |
| • Tobacco products |
| • Alcohol biomarkers |
| • Trichloroacetic acid |
| • Total urinary bisphenol A |
| • Phthalate monoester metabolites |
| • Hydroxypyrene |
| • Organophosphate pesticides |
| • Heavy metals |
| • Persistent organic pollutants |

**(1)** RNA will be collected in parental blood; RNA in infant is not included in the core sample collection

### 2.9.4 Analysis of biosamples

Although indicative examples of analyses relevant to the research themes and hypotheses of Life Study are provided, assays will not be undertaken immediately after collection.[13]

Expert opinion will be sought regarding the scientific opportunities and optimal use and maintenance of the biosample resource, taking into account the expected technology development curve. Specifically, advice will be sought about the timing of the analysis of samples collected in Life Study and implications of proceeding with or deferring analyses until the sample collection is complete across all relevant participants. Areas that are potentially of great importance for Life Study, but where the high-throughput technology is still developing, are exome and whole genome sequencing, epigenomics and the microbiome. The cost of these technologies is likely to fall significantly in future, and the requisites for the delivery of high quality will become better understood, so it may be prudent to wait until these technologies have matured before processing Life Study samples. The experience of UK Biobank - currently extracting DNA from samples as a prelude to genome wide analyses – will be very useful to Life Study.

An important goal will be to generate derived non-depletable data, which could be made accessible to the research community as early as possible, however consideration will also be given to the retention of samples long term for future analyses that are as yet undefined.

### 2.9.5 Access to biological samples

Access to biological samples will be carefully considered to ensure maximal utility is made of a finite resource. A specified time to process and analyse data will be agreed and biological samples will be provided to approved investigators on a cost-recovery basis.

The following principles for access will be observed:

- All research on and access to samples, and data derived from samples, will be in keeping with the consent obtained and with Life Study ethics, governance and data access policies, as will publication of research results and data
- All requests for access to biological samples for specific research proposals will be assessed by an Access Committee according to a pre-defined set of criteria.
- Where specific assays are identified as essential for the delivery of the Life Study primary objectives, these will be given appropriate priority.
- Data derived from assays will be deposited in the Life Study resource where appropriate. Unnecessary duplication of assays will be avoided.

[13] These principles are similar to those underlying the development of the UK Biobank biosamples resource.

- Following approved requests for access to biological samples, assays may be organised by the Life Study scientific leadership team to ensure appropriate quality control and feedback of results.
- It may be appropriate for samples to be analysed overseas, for example where the best laboratory to perform the analysis is based overseas or where the sample analysis is being carried out as part of an international collaboration.
- Any commercial access to samples will be on condition that the results are returned to Life Study within a fixed time and the findings published in full in open access peer reviewed media.
- Any samples left over after laboratory analysis is complete will be returned to Life Study where possible.

## 2.10 Record linkage

The main individual person-level record linkages[14] for which consent will be sought in this first sweep are described here:

- Primary care and hospital health records including visits to GPs, hospital admissions and attendance, records of specific conditions such as cancer or diabetes, and prescriptions;
- Permissions to trace participants through health-related demographic registers and to 'flag' them against future migrations or death;
- Assisted conception records held by the Human Fertilisation and Embryology Authority (HFEA): for those who have had medically-assisted conceptions
- Benefits and employment records: administrative records on benefits, tax credits, employment support programmes, as well as earnings, pension contributions and employment histories
- 2011 Census data for participants and, if possible, their households
- Education records including the National Pupil database (NPD) and the Pupil Level Annual Schools Census (PLASC) database, as well as further and higher education records
- Mobile phone records: mobile phone operator records on mobile phone traffic, including timing and duration of calls, texts, and data transfer

It will be important to link to a range of neighbourhood (postcode level) variables, such as deprivation scores (e.g. Index of Multiple Deprivation (IMD), Townsend and Carstairs indices), local unemployment rates and housing tenure. There will also be linking to environmental data at postcode level, for example to existing measures of air and water quality. Linkage to individual address level derived variables, for example to import data around housing exposures or interventions or finer level environmental exposures, is currently possible in Wales and may well extend across the UK.

Additional opportunities for linkage to local commissioning datasets are being explored within the first Life Study Centre.

[14] Equivalent linkages will be sought in England, Scotland, Wales and Northern Ireland

### 2.10.1 Consent to record (data) linkage

Consent for record linkage will be sought at the initial pregnancy visit. The Life Study record linkage working group explored different models for consent with key academic stakeholders and data controllers, including representatives of government departments.

The acceptability of record linkage was also evaluated through the consultative conference and public engagement activities, including focus groups, undertaken during the pilot phase of Life Study. Specifically, it was decided that linkage to Ministry of Justice and police records would not be part of the current data collection sweep.

### 2.10.2 Processing, storage and access

Life Study is developing the processes required to manage the anonymisation, storage and linkage of datasets. It is anticipated that Life Study will centrally manage the anonymisation of different kinds of data and assignment and management of identifiers.

### 2.10.3 Wider record linkage collaborations

Life Study is working closely with the UCL and Swansea University components of the Farr Institute of Health Informatics Research (a UK network of centres of excellence in health informatics, financed by an MRC led group of ten funders) and the ESRC funded Administrative Data Research Centres, which are facilitating record linkage to other routine and administrative records in England, Wales, Scotland and Northern Ireland.

## 2.11 Birth Component Home Visit protocol

The Life Study Centre visit protocol will be adapted for use as a home visit interview for the Birth Component, taking into account the need to ask about pregnancy and birth retrospectively. There will be no biological samples or biomedical measures in the Birth Component. Piloting for the Birth Component home visit will be undertaken prior to recruitment starting in 2015.

## 2.12 Enhancements to the core protocol

In addition to the core-funded scientific protocol, funding may be sought by research teams to undertake ‘enhancements’ to the core data collection to fulfill specific research objectives. These enhancements may involve all participants or a sub-sample of those participating. Although each Life Study Centre will operate a common protocol, enhancement studies may be implemented in a limited number of centres.

Applications to enhance data collection for a specified purpose will be approved by a subgroup of the SSC as described in the ‘Life Study Enhancements Policy’ and this also includes review by the Life Study Strategic Advisory Committee (SAC). Proposals will be

considered against an agreed set of criteria that include considerations such as scientific rationale, impact on the core Life Study objectives and design, participant burden, feasibility, ethics and governance issues, and funding. Enhancements require additional funding and applications to funding bodies are likely to be necessary. A substantive amendment for any approved and funded enhancement study will be submitted to the Research Ethics Committee to seek approval for any research activities that are outside the scope of the main study ethics approval.

The Infection and Immunity Enhancement (PI: Professor Peter Brocklehurst; Wellcome Trust funded) proposes to collect detailed information regarding the pregnancy and delivery from the maternity unit, together with biological samples (e.g. umbilical cord blood samples, vaginal and faecal microbiome) in order to contribute to the understanding of infection and immunity in the fetus and neonate. This was the first enhancement to be approved by Life Study SSC, SAC and the Research Ethics Committee and funded through a Strategic Award made on 26th April 2013. Pilot work started in February 2014 in preparation for inclusion in the main phase protocol.

The Non-Resident Fathers and Resident Fathers/Partners Enhancement (CoPIs: Professors Carol Dezateux and Kathleen Kiernan; Nuffield Foundation and ESRC funded) proposes to augment recruitment and retention of fathers and partners. This was the second enhancement to be approved by Life Study SSC, SAC and the Research Ethics Committee and funding was awarded on 31st March 2015.

## 2.13 Follow-up and future data collection after the first year

It is intended that all parents and children participating in Life Study will be followed up at later ages with further questionnaires and biological samples. Future data collection sweeps could record changes to family circumstances, longitudinal growth and development, and evaluate key outcomes, such as neuropsychiatric conditions, vision, asthma, educational achievement and social identity. Further follow up of participants would include linkage to relevant electronic records (see above), as well as web-enabled data collection (augmented by telephone, computer, or reply paid questionnaires) to maintain contact with children and families after the face-to-face centre and home visit(s).

# 3 Ethics, consent and confidentiality

## 3.1 Ethical, Legal and Social Issues

Ethical, legal and social issues can be complex and critical to the success of a contemporary large-scale epidemiological study. Rapid advances in biotechnology, information technology and the clinical and social sciences, and changes in societal expectations present a challenging array of ethical, legal and policy issues.

Life Study will be the largest UK study of pregnant women and their partners and babies; it will collect information, biological samples for a biobank resource, and link to routine data explicitly from the outset. The study is likely to encounter a range of complex ethical issues that will not have been encountered in the previous national birth cohort studies, which did not recruit in pregnancy.

Although external research ethics and governance approval processes ensure that the study design is ethically acceptable, Life Study requires mechanisms for adapting policies to address ethics issues arising over the lifetime of the study, and to respond to changes in the societal and legal context. Life Study will need to respond to specific issues, such as arise through public involvement activities or the implications of specific research findings.

## 3.2 Life Study Ethics and Information Governance Framework

A Life Study Ethics and Information Governance Framework[15] has been developed to set out the Life Study approach to ensuring the ethical conduct of the study and management of the resource within the broad context of the Life Study relationship with participants, with research users, and with society.

Issues considered in its development included:

- Relevant activities/reports by other organisations, including Life Study funder policies;
- Legal requirements relating to the management of Life Study information and samples;
- Obtaining future-proofed consent for different types of data, including record linkage;
- Obtaining consent from different types of participant, such as mothers, partners and babies (including consideration of mental capacity to give consent);
- Children attaining capacity to consent during the timeframe of a longitudinal cohort study;
- Feedback of incidental findings;
- Recruitment and collection of information and samples from fathers and partners;

[15] This is available as a separate report for download on the 'Resources' page of the Life Study website www.lifestudy.ac.uk.

- Principles of good information governance for participant information and biological samples collected, including the management of data security and access
- Principles of access to the biological samples, which are a depletable resource
- Commercial or international access to the data, or requests for access for non-research purposes e.g. related to issues of paternity.

## 3.3 Life Study Advisory Group on Ethics

A Life Study Advisory Group on Ethics has been established. See the Life Study Ethics and Information Governance Framework for more information.

## 3.4 Key ethical concerns in the first 'sweep' of Life Study

Two key ethical concerns have been addressed for the initial contact with participants are outlined below:

### 3.4.1 Initial contact: Section 251 approval

An important consideration for Life Study was the initial contact with pregnant women or mothers to tell them about the study and invite them to take part. Every woman who is eligible should have an opportunity to find out about the study and decide whether to take part, including women who are traditionally considered to be hard-to-reach, for example women who book or transfer late into a maternity unit, who do not understand English or have low literacy skills.

As the Life Study design is intended to allow research findings to be placed within the context of a nationally representative population of very young children, it is vital to have information about the characteristics of non-responders to understand the potential for bias and to pro-actively recruit from under-represented groups. Anonymised or aggregated details (e.g. age, ethnicity) of all pregnant women or mothers are also needed to create the statistical weights to be used in analyses of the study data.

Life Study successfully sought approval under Section 251 of the NHS Act 2006 for a 'trusted third party' to manage invitation mailouts (principally to the Birth Component sample) on behalf of Life Study, as well as to collate individual-level data from birth registrations to be used by Life Study ONS approved researchers for the analysis of non-response.

### 3.4.2 Feedback to participants

Providing health-related feedback within a research study has significant risks when tests are innovative, and test results may not be clinically relevant or readily interpretable with regard to the health implications for the individual. Participants will be clearly informed that Life Study is a research project and that they will not receive feedback or results from many of the novel tests undertaken during the visit.

# 4 Managing the Life Study Resource

## 4.1 Information systems to manage appointments and the data resource

Life Study will develop secure and robust Information Systems that can:

- Capture and store data about participants throughout their involvement in the study
- Capture data directly from participants
- Manage flows of data to and from national institutions, e.g. ONS, UK Data Archive
- Store and manage data for analysis and reporting.

### 4.1.1 Key components of the system

**Participant Identification & Enrolment:** The systems in use will begin by recording contact details and basic information from pregnant women and partners in maternity units, or babies and their families sampled through birth registrations.

Midwives will use the **Maternity Unit IT systems** to identify eligible participants. Life Study Centres will be commissioned at accessible sites proximal to their 'feeder' maternity units.

An appointment scheduling system will manage the scheduling of Life Study Centre appointments. This may be sited with the fieldwork or another agency.

The **Birth Registries** are held by the Office for National Statistics (ONS) in England and Wales, the General Register Office for Scotland (GROS) and the Northern Ireland Statistic and Research Agency (NISRA).

A **Fieldwork Agency** will be commissioned to manage contact details, appointment scheduling and home visits for the Birth Component.

The **Data Linkage and Extract Service (DLES)** within the NHS Health and Social Care Information Centre may act as a **trusted third party** holding contact details held under Section 251 approval to inform list-cleaning and invitation mailouts for initial appointments.[16] Key **health status services** that will support recruitment include the Patient Demographics Service (PDS) and NHS Numbers for Babies (NN4B; also sited within the PDS).

**Participant Record Management System:** After consent, patient details will be held within a centralised record system to facilitate follow-up.

[16] Section 251 permission was obtained for this, however in the final design NHS Trust systems were utilised by NHS-employed Life Study staff within each Centre to manage the contact details and mail outs.

**Participant Data Collection:** Information systems will include direct collection of data at interview, from measurements taken during the Centre visit or through self-complete computer-assisted questionnaire (survey).

Data collected through all sources, including the Life Study Centres and home visits, will be returned to a central **Data Management System** for analysis and reporting, prior to archiving for access by research users. The **Biorepository** and **UK Data Archive** represent the final archives for data, measures and biosamples collected through Life Study.

### 4.1.2 Specific requirements

Several important components were highlighted as important for inclusion in the final information system, following testing tested in the pilot study:

- **Consent management:** While electronic consent forms would allow for the recording of cryptographically bound signatures that comply with UK and EU legal requirements, it was ultimately found simpler to comply with Research Ethics Committee requirements and to provide participants with a paper copy of this form.
- **Accessibility:** Information systems will be accessible for users with disabilities and compliant with the Disability Discrimination Act.
- **Tracking the Centre visit:** During each visit, the data, physical measurements and biosample collections will be tracked effectively and associated with the correct participant records.
- **Survey management:** All measures used for Life Study will be described within a metadata catalogue, which will be available to the research community for reference in support of any data access requests or protocol review.
- **Biosample management:** All biological samples will be tracked and recorded from point of collection to the Life Study biorepository to comply with the Human Tissue Act.
- **Asset management:** Study instrumentation, computer hardware, peripherals and software will be recorded in an asset register to support workflow (e.g. calibration reminders and fault handling).
- **Real-time dashboards:** A central management dashboard will allow the study team to examine performance indicators in near real-time, and to identify unexpected issues in operational aspects of the study.

### 4.1.3 Security standards and governance procedures

Security of personal data is vital to Life Study. Life Study Information Systems will have different security zones with different requirements for information security depending on the nature of the data being collected or held. Handling of non-aggregated personal datasets will be contained within security zones that comply with best practice information security, independently assured to meet the ISO 27001:2005 information security management systems (ISMS) standard, compliant with the NHS Information Governance Toolkit and assessed as IL2 (Business Impact Level risk assessment). User and role based

access control will ensure that only personnel who require access to specified files and datasets are granted permission. Data transfer will be in an encrypted format using AES256 encryption standards. As necessary, additional security zones will be introduced, e.g. for fieldwork agency and biorepository services.

## 4.2 Expectations of the Life Study resource

Management of the resource must respect the undertakings to participants and funders, the principles contained in relevant Life Study policies, and the anticipated expectations of participants, researchers, funders and society:

- **Participants** will expect a high degree of data security and confidentiality around sensitive or personal data and samples, and the resource to be managed in a way that is consistent with the participant consent and regulatory ethics approvals;
- **Researchers** will expect data to be of high quality, up to date, validated and as complete as possible. Data should be accessible and useable;
- **Funders** will expect high quality data to be made available as early as feasible, with as few restrictions as possible, and maximising the value of the data for research and for public benefit
- **Society** will expect research data and samples to be used for the public good, confidentiality to be respected, proportionate governance, and for data and samples to be kept secure, safeguarding them for future use.
- **Public bodies** such as the National Research Ethics Service, the Confidentiality Advisory Group of the Health Research, and the Human Fertilisation and Embryology Authority, will expect Life Study to meet certain standards; and obey relevant laws such as the Human tissue Act and Data Protection Act.

## 4.3 Data Types

The types of data and the principles for their storage and access outlined here:

- **'Questionnaire' data** from participants (including self-complete questions and interviews)
- **Biomedical physical measurement data**, for example anthropometric and vision measurements collected at the Life Study Centre visit
- **Biological samples**, such as blood, urine and placenta
- **Paradata**, i.e. data concerning the process of collection of information or samples from individual participants
- **Metadata**, i.e. catalogue data on the questionnaire instruments or biomedical assessments chosen, or on the collection and storage requirements for biological samples
- **Linked data**, for example routine health and other administrative data obtained through record (data) linkage
- **New secondary data or derived variables**, for example data derived from statistical analysis of Life Study data or from assays on biological samples.

Table 6: Time points for data and sample collection

| Visits | Pregnancy | Baby aged six months | Baby aged twelve months |
|---|---|---|---|
| **Birth Component** | **None** | **Home visit** | **Web / postal / phone questionnaire** |
| | | • Questionnaire data from mother and partner/father<br>• Retrospective pregnancy data<br>• No biomedical assessments or biological samples. | • No biological samples. |
| **Pregnancy Component** | **Life Study Centre visit** by mother and father/partner | **Life Study Centre visit** by mother and baby | **Life Study Centre visit** by mother and baby |
| | • Questionnaire data<br>• Physical/biomedical measures<br>• Biological samples. | • Questionnaire data<br>• Physical/biomedical measures<br>• Biological samples. | • Questionnaire data<br>• Physical/biomedical measures<br>• Biological samples. |
| | **Birth (hospital)** | | |
| | • Biological samples. | | |

### 4.3.1 Disclosure risk

Care will be taken to safeguard against any disclosure of personal data or breach of confidentiality of participants in Life Study. The storage location, security safeguards and arrangements for access will vary according to the level of disclosive risk associated with different data types:

- **Non-disclosive** and **non-sensitive data** (including in combination): these have a (very) low risk of disclosure will be deposited with the UK Data Archive and available to researchers for download after on-line user registration.
- **Moderately disclosive or sensitive data** (e.g. postcodes): require a special license for access. Additional steps to remove/pseudonymise identifiers may be required.
- Biological samples and data that are **disclosive or sensitive** (including some paradata): accessed via a specially constituted Data Access Committee applying an agreed set of criteria for the assessment of access applications.

### 4.3.2 Usability of data

Processing of data for access by researchers will depend on the usability of data. Broadly, Life Study data will include data that:

- are useable by researchers with a minimum of processing (this minimum might include cleaning and anonymisation before wider distribution together with sample weights);
- require additional (often expert) processing to produce useable data variables that can be incorporated in or otherwise linked to the existing Life Study database. This processing may involve data manipulation to produce derived summary variables from data collected directly in the Study (e.g. of socio-economic status or educational qualifications), or from more complex coded data collected initially through record linkage (e.g. Hospital Episode System data);
- are produced from laboratory analysis of materials such as biological samples and which may require further processing of variable complexity to become useable.

## 4.4 Storage of data and samples

Arrangements for data deposits or storage will be appropriate to the sensitivity and disclosive risk associated with the data. Different archives will be selected as appropriate to the sensitivity of the data, for example:

- **Non-disclosive and non-sensitive data** will be deposited with the UK Data Archive.
- Moderately/highly disclosive or sensitive data will be deposited in a secure data archive.
- **Large and complex datasets**, such as derived from genome-sequencing, may require specialised facilities, such as a repository for bioinformatics data.
- **Biological samples** will be stored in a secure biobank (biorepository) with a back-up held at a separate geographical location.

Data may be stored in separate locations or in one physical store but with different data-handling protocols. Data extracts would be produced to service different classes of request. Data will also be stored in a geographically separate secure back-up location.

### 4.4.1 UK Data Archive

The UK Data Service hosts an archive containing key national and international survey data collections, international databanks, census data and qualitative data. It provides secure access to data of high sensitivity. The majority of data are fully anonymised and while accessible to researchers are not publicly accessible. Several types of data are deposited in this archive and made available including quantitative, qualitative, and multimedia data as well as non-digital material (See http://ukdataservice.ac.uk/get-data/about.aspx).

## 4.5 Data Release

By mid-2016, should recruitment attain the estimated 50% on which these figures are modelled, Life Study will have recruited up to 16,000 pregnant mothers, 11,000 fathers/partners, and - c 16,000 babies - into the Pregnancy Component and – depending

on the outcome of the longitudinal pilot of the opt-in sampling strategy - up to 10,000 mothers with babies into the Birth Component. It is anticipated that a single dataset from Phase 1 (pregnancy and six months data) will be released with sample weights in early 2017, following data cleaning and annotation.

User engagement is essential to prepare and support data users so in preparation for the release of this integrated Phase 1 dataset, a 'beta test' dataset will be released together with descriptive metadata to enable researchers to familiarise themselves with the Life Study data variables and study design. A process will be developed for determining the appropriate timing and content of such datasets and the materials, training and communications necessary to prepare the scientific community for their release. An additional consideration relates to the completeness of Life Study datasets in terms of the proportion of the participants recruited and the completeness of their follow up in any given data release. For example, if data collected in a subset of Life Study participants are released before all participants have been recruited across the country, any constraints on using data that specifically relate to that subset need to be fully understood and addressed. The frequency of subsequent data release remains to be determined and will ensure as early and complete access to the data for the research community as feasible.

### 4.5.1 Questionnaire and biomedical assessment data

Questionnaire data and some biomedical data will be released into the UK Data Archive, to be made available to users on an appropriate basis, with licensed access for sensitive or disclosive data.

### 4.5.2 Large-scale data and bioinformatics

Some types of biological sample analyses, such as genome sequencing, will create large volumes of complex data, which will require further analyses to provide meaningful variables for release. The storage of such data may be best managed through a bioinformatics resource. These data will need to be linked to the core Life Study datasets held at the UK Data Archive and will need additional work to ensure they are accessible to users.

## 4.6 Data access policies and practice

Life Study will be building on the UK's established infrastructure for access to birth cohort and other longitudinal data resources, which ensures that appropriate safeguards are in place to minimise risk of disclosure and to respect the consent and preserve the confidentiality of participants.

In 2008, the World Health Organization and the Wellcome Trust initiated discussions around a common Code of Conduct on the sharing of data of public health importance. In 2010 this code was revised at Foggy Bottom and in 2011 the major research funders put out a joint statement on sharing research data to improve public health (signatories include the Wellcome Trust, ESRC and MRC).

More recently the Expert Advisory Group on Data Access (EAGDA) was established by the Wellcome Trust, MRC, ESRC and CRUK to provide strategic advice on the emerging scientific, legal and ethical issues associated with data access for human genetics research and cohort studies. EAGDA is considering data access committees and incentives for data sharing, and has recently developed a statement for EAGDA funders on the risk of re-identification of anonymised research participants from genomic and other data.

Some data from the biomedical measures, including videos of mother and child interaction, may require special access arrangements as the identity of mother and child cannot be masked.

## 4.7 Framework for Managing, Sharing and Accessing the Data Resource

### 4.7.1 Introduction

A preliminary Life Study Data Access Policy was developed in 2012. A draft framework for managing, sharing and accessing the Life Study data resource is currently being developed; the Data Access Policy will be revised as required. The framework and policy set out a number of principles and undertakings relevant to data access.

### 4.7.2 General principles for the management of participant data and samples

The Data Access Policy will be based on the following draft principles:

- The principles for access to LS data and biological samples, including any consideration of protected or preferential access, will take into account the three key principles identified by funders in the Foggy Bottom agreement, namely that access to the data and biological samples will be equitable, ethical and efficient[17]
- Life Study data will be made available using the 'intelligent openness'[18] principles to inform the delivery of the Life Study datasets to users
- The level of scrutiny used to assess applications will be proportionate to the nature and scale of the research project, taking into account the depletable nature of biosamples, any

[17] http://www.wellcome.ac.uk/About-us/Policy/Spotlight-issues/Data-sharing/Public-health-and-epidemiology/WTDV030690.htm

[18] Royal Society report 'Science as an Open Enterprise'

proposed contact with Life Study participants, potential implications for Life Study resources, and any ethics or other potentially contentious issues.

- A legally binding agreement will be required in certain instances, for example for access to sensitive and disclosive data or biological samples.
- Only members of the Life Study team will be allowed to contact study participants directly; strict guidelines regulating such contact will be required.
- Anyone given access to the resource must undertake not to try to identify individual participants, or compromise the security of the data or the anonymity of participants.
- Access to Life Study biomedical samples will be carefully considered to ensure maximal utility is made of a depletable resource.
- Approaches to access Life Study data and samples should build on existing practice and reduce unnecessary duplication and competition. All information derived from Life Study data and/or samples (including any secondary or derived data) must be submitted to the Life Study team for inclusion in the Life Study central database.
- There will be no onward sale of Life Study data or samples. All information derived from access to the Life Study resource (including derived variables and data derived from statistical analysis) must be submitted to the Life Study team for inclusion in the Life Study database. There will be accompanying documentation sufficient to identify the analyses undertaken and interpretation of the results, and a brief description of the methods used.
- Under the current funding arrangements for Life Study, researchers given access to biological samples or modified datasets will be expected to meet all of the associated costs.
- All users of Life Study data and/or samples must appropriately acknowledge the original study in their reported and published findings.

# 5 Communications, engagement and participant and public involvement

## 5.1 Importance of Participant and Public Involvement (PPI)

Communications, engagement, and especially participant and public involvement (PPI), are recognised as crucial to the success of Life Study. Participants – children and families – are at the heart of the study and key to delivering a study of this scope and ambition. With this in mind, a dedicated strategy has been developed and is being implemented across the study to ensure a robust approach to communications, engagement and PPI. The Life Study Communications and Engagement Strategy has been published as a separate document and can be downloaded from the 'Resources' page on the Life Study website.[19] The main elements of this Strategy are summarised in this section.

The key audiences targeted by the Strategy are:

- Participant audiences (including potential participants, families of potential participants, peers/friends of potential participants)
- Healthcare professionals (including hospital trust leadership, maternity unit staff, community healthcare providers, GPs)
- Researchers and academia (including other cohorts, scientific committee members, NHS research networks, educators)
- Funders
- Policymakers and political influencers (including Chief Scientific Advisor, Council for Science and Technology, ministers and officials in government departments with a major interest in Life Study, MPs, select committees, regional government and local authorities, local overview and scrutiny committees, think tanks)
- Media (including local and national mainstream media, targeted and trade media)
- Data services (including UK data archive)
- Third sector (voluntary, not-for-profit and community groups)
- Businesses (such as those marketing maternity and baby clothes, toys etc)
- Life Study providers (such as fieldwork agencies and business analysts)
- and the general public.

### 5.1.1 Participant audiences

Participant audiences require a distinct approach compared to the other target audiences as communications activities seek to aid recruitment and retention, and engender a sense of ownership of the study rather than just increase awareness of and support for the study. Developing a positive image for Life Study amongst potential study participants is a primary

[19] www.lifestudy.ac.uk

objective for the first phase of the study. In later phases, communications activities will be focused on information provision to secure continued participation and maintain participant engagement. Therefore, the approach is underpinned by four strategic principles that ensure that, whilst being flexible and responsive to diverse audiences, all elements of communications, engagement and PPI can be consistently and holistically delivered to meet participant needs and the key study objectives of recruitment and retention.

## 5.2 Communications, engagement and PPI strategic principles

### 5.2.1 Audience Led

All communications are audience-led and, wherever possible, evidence-based; this audience focus extends into all aspects of study design. Life Study's strategic approach is grounded in understanding our audiences and then tailoring communications to respond to those audiences' specific interests, needs and concerns.

Life Study has already been implementing a range of PPI opportunities that focus on both our communications as well as obtaining audience feedback on the study design. Research with audiences is undertaken formally (that is, as a structured programme of qualitative audience research) and informally (such as informal 'soundings' with key representatives from target audiences). Dedicated PPI groups will be an ongoing resource to support involvement (see 'Next steps in PPI').

Examples of work being done to develop audience-led communications and embed evidence from PPI in other aspects of the study design include:

- crafting messages based on audience research and PPI activity, rather than on internal Life Study views
- using specific examples of potential research topics and findings to demonstrate value of the study to participants, as requested by focus groups
- refining study questionnaires in line with specific feedback through focus groups and the study pilot
- designing the facilities at Life Study Centres based on participant requirements
- using communications channels that are already used and trusted by target audiences, including online
- testing public-facing materials with participant audiences and members of the public to establish that they are fit-for-purpose, accessible and will achieve maximum impact.

### 5.2.2 Phased

Life Study audiences are taken on a journey that supports full understanding, commitment and participation. It is important that Life Study ensures participants are given the opportunity to fully understand what they are committing to in Life Study. That is why communications and engagement activities will be approached in a phased way, creating

audience journeys that introduce layers of complex information so as not to overwhelm participants. Examples of strategic phasing include:

- developing audience messages to take them on a journey to participation and/or commitment – for example, using multiple formats for communicating (leaflets, postcards, online) and presenting different pieces of communication to participants at different times
- concentrating communications on key study objectives (recruitment, data-sharing) at different points in the study
- concentrating on milestones in parents' and babies lives and understanding the importance of this special time.

### 5.2.3 Building Trust

Trust is the foundation upon which all other communications asks are made and imperative to participation in the study. The building and maintenance of trust is relevant to all audiences and the foremost communications task throughout all phases of Life Study. Examples of how we are already working to build trust with our audiences, especially potential participants and the public include:

- seeking and displaying endorsement from organisations and brands recognised and trusted by potential participants (for example, NHS Trusts with which we have been working)
- up-to-date provision of accurate information – progressing plans to update our Life Study website
- recognising the complexity of Life Study, using face-to-face communications where possible
- tone – speaking to all supporters and participants in language that places them on an equal status. No hyperbole or jargon. Communications are pitched at a level that the majority can understand
- thanking every participant and supporter properly, such as through the thank you letters following the pilot study.

### 5.2.4 Inclusiveness

Life Study wants to be representative of the rich mix of people living in the UK today. This means that Life Study's communications and other aspects of the study design must not exclude any potential participants or supporters.

Examples of how we are already aiming to be inclusive include:

- PPI work to understand the needs of participants and the public and making sure that materials and study design are responsive to those needs
- Imagery showing a diversity of ages, ethnicities and family units
- Language – for example, use of 'partners' and not 'husbands'
- Using a guide reading age of around 12 years for all participant communications
- Planning for provision of interpretation and translation services.

## 5.3 Engagement and PPI activities to date

The initial PPI activities focussed on the pregnancy component.

### 5.3.1 Focus group meetings to support Life Study branding exercise

An initial consultation in March 2012 sought public feedback on the newly created study name, brand and logo. The Life Study communications manager field-tested three different visual designs in focus group meetings held in London and Birmingham[20] with the study's primary target audiences: pregnant women and their partners. It was considered critical to have input from the study's target audience both from within and outside of London – with a mixture of women and men from different ethnic and social backgrounds. These focus group discussions provided validation for the study name, look and feel.

Another important outcome of this consultation was the development of a working relationship with the Avon Longitudinal Study of Parents and Children (ALSPAC) young peoples' group, who were also asked to provide views on the branding. This relationship will facilitate the development of similar participant involvement initiatives for Life Study.

### 5.3.2 Lay representation on the Record Linkage Scientific Working Group

There is a lay representative (parent) member of the scientific working group that is deliberating the approaches and timing being proposed for consent to data linkage within the Life Study cohort. Consideration has been given to information provision to participants, the appropriate wording of consent statements and the need for regular review.

### 5.3.3 Ongoing public involvement representation on the LSSAC

Within the Life Study governance structure the Life Study Strategic Advisory Committee (LSSAC) is responsible for providing independent assurance that Life Study is delivering against its core objectives. The LSSAC directly advises on, and challenges, the strategic development and delivery of the project, advising the funders on key areas where they facilitate the effective delivery of the project.

The membership of the LSSAC includes provision for two lay representatives with relevant expertise in the involvement of parents, children and young people in research, and they are able to advocate on behalf of participants in the study on an ongoing basis. As an example, the LSSAC and lay members were involved in making recommendations regarding the overarching communications, engagement and PPI strategy for the study.

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[20] Held with the Coram Community Centre in Mecklenburgh Square, London and Gateway Family Services in Birmingham respectively.

### 5.3.4 Stakeholder knowledge-gathering interviews

In March and April 2013, the Life Study team conducted a number of knowledge-gathering interviews with stakeholder representatives. The objectives were two-fold: to understand the audience from which the interviewee was drawn (for example, the research community) and then to draw on the experience of the individual in engaging and involving participant and public audiences in similar studies or related fields of work.

Twenty interviews were conducted in total and the information gathered was both of strategic significance in informing the overarching approaches and principles, as well as practical significance in informing specific messages, tools and channels for participant and public audiences.

This evidence was then used to inform the planning of focus groups and in-depth partner interviews with participant representatives. This allowed for the concepts, key messages and tools that were developed for focus group testing to be based on existing knowledge, experience and best practice from other cohorts.

### 5.3.5 Focus group and partner in-depth interviews on Life Study concepts and recruitment

Across May and June 2013, 12 focus groups, of approximately six to eight pregnant participants were each conducted over a two hour session. Six of the groups were held with the black and minority ethnic (BME) group audiences identified as priority target audiences for phase one of the study: Indian, Pakistani and Bangladeshi groups. The other groups were held with core or mainstream audiences, which included black African and African/Caribbean participants. Women recruited were between 14 and 36 weeks pregnant. A spread of participants with differing marital status, working status and maternal age were recruited.

Alongside the group work, 12 couple and family depth interviews were conducted; six of these were with BME audiences. The family depths for BME groups included the couple and the mother or mother-in-law of the expectant woman. The BME sessions were conducted in multiple languages for the mix of language requirements in any one group. For example, where a group included both first and second generation Pakistani women, the group was conducted in both English and Urdu to cater for all participants' language needs.

The sessions investigated participant audience responses to:

- the 'idea' of Life Study
- the best communications channels to use for reaching participants
- how to explain the study to participants / language use
- other key messages and priority information

- any alienating concepts that should be considered in the study design (for example, biological samples and specific questions)
- practical considerations of the 'ask' of participants (for example, travel requirements and childcare arrangements)
- how to build trust in the study through partnerships and spokespeople.

The outputs of this research have already been invaluable in assisting the design of study materials, reviewing the study protocol (including specific questions and samples) and informing the best channels through which to recruit participants to the study pilot which ran during November 2013.

In conjunction with the outputs of subsequent PPI activity used to further refine study elements, this focus group research continues to be used into the main phase of the study.

### 5.3.6 Existing cohort member discussions

Members of the Life Study team visited the Born in Bradford (BiB) annual engagement event, the Teddy Bears' Picnic, at the end of May 2013. This provided an opportunity to learn directly from existing cohort members about their experiences of being part of the cohort, what prompted their initial involvement and what keeps them involved. This is an example of the more informal PPI and evidence-gathering that Life Study conducts.

Team members were able to have one-to-one informal discussions with cohort members against the backdrop of the community roadshow-style event and gather firsthand accounts of participant experiences. This information has been collated with other audience research and is used in all decision-making processes.

The Life Study team continues to stay in regular contact with the teams from BiB and other cohorts, including through the Cohorts and Longitudinal Studies Enhancement Resources (CLOSER).

### 5.3.7 Cognitive interviews on study protocol questions

In May and June 2013, the Life Study team undertook a cognitive testing exercise on some of the proposed study questions to ensure consistency in participant understanding of questions that had not been used elsewhere previously.

The cognitive testing exercise allowed for participant representatives to feedback on their experience of the questions tested and informed any modifications to those elements of the questionnaire. This feedback directly influenced the further use of those questions in pilot testing.

### 5.3.8 Participant interviews – communications (look, feel and language)

Alongside the cognitive testing, the Life Study team tested some of the communications elements that had already been shaped and focused through previous PPI work. The elements tested with 39 individuals - a mix of pregnant women, partners and mothers of young babies - were:

- design palettes
- imagery
- communication channels
- priority information
- language and accessibility.

The feedback has been collated with other information gathered through the various PPI channels and has been used in development of participant and study materials.

### 5.3.9 Testing public engagement methods and activities

At the end of June 2013, as part of the MRC's centenary celebration events, UCL hosted a science fair and Life Study presented a stall of activities to visitors.

The event was an opportunity for Life Study to test some of its engagement approaches and further the team's understanding of what interests the public and how to position Life Study for maximum impact in the communities it is trying to reach.

There was an overwhelmingly positive response to Life Study activities from members of the public visiting the free event and the activities will be used again at future community engagement events locally around Life Study Centres. The activities were specifically designed to demonstrate Life Study concepts as follows:

- Height fortune-teller – using height charts to predict children's future heights
- Life Study passport children's activity book – including genetics and environment questions and the child's Polaroid picture
- DNA modelling – using sweets to make double-helix models
- Life Study presentation

### 5.3.10 Core pilot processes and materials

In November 2013, the Life Study team piloted the study with a small number of participants. All of the learning from PPI and associated activity up to then was used to inform the design of the pilot, the recruitment processes, materials and aspects related to participant experience.

Most elements of the study design, excluding collection of some samples, were tested and participants gave feedback on:

- Recruitment processes and pathways
- Recruitment materials
- The clinic appointment, including
  - Experience, such as waiting times, facilities, length of appt and staff
  - Specific activities, including interviews and questionnaires
  - Travel and travel expenses
- Post-visit, including
  - Feelings about the whole experience
  - Discussions with others such as GP
  - Any behavioural changes

This feedback has been used to inform the study design and materials for the main phase. Piloting most elements in situ and then collecting comprehensive feedback from participants has provided assurance that PPI outputs have been fully embedded in the study design as a whole. The previously fragmented feedback on elements of the study that were presented out of context has now been validated through this process.

### 5.3.11 Enhancement pilot study materials and processes

In addition to the core study elements, Life Study has received funding for an enhancement study specifically focused on the microbiome and infection and immunity. The pilot for the infection and immunity enhancement will test with participants the sample collection that could not be tested in conjunction with the core pilot. Participant questionnaires have been developed and feedback from this pilot is expected to further the team's understanding of the acceptability of requesting specific samples from pregnant women and new mothers, barriers to involvement and any refinements or additional communications needed to support participation. Maternity staff are also being asked to give their impressions of the likely barriers to women's participation.

Together with all other PPI activity and outputs, the feedback gained through the infection and immunity pilot will provide essential information to prepare Life Study for working with participants in the main phase and being responsive to their needs.

## 5.4 Development of the main phase materials and audience testing

It is important to Life Study that all of the information gathered to date from participant representatives has been interpreted correctly and that the team is assured that it has acted in the best interests of participants in all respects.

With this in mind, the draft main phase materials that were based on extensive audience research and study piloting, were tested with pregnant women and partners on site at one of the first NHS antenatal clinics through which main phase participants will be recruited.

Pregnant women, and partners if present, were approached in the same way that recruitment to Life Study is currently planned. The design of this interaction was considered in an attempt to make the feedback authentic and as indicative of future participants' reactions as possible.

Pregnant women and partners were presented with draft posters, leaflets, postcards and participant information sheets and asked by members of the team to comment on:

- Content – including information provision; Is there anything missing?
- Design – including imagery, format and paper stock
- Accessibility – including language, fonts and alternative format requirements
- Uptake – reactions to the materials and whether from the material presented, they would be likely to make a decision to participate in the study.

The pregnant women and partners involved were also asked to share their demographic information so that any trends in responses could be explored.

All of the feedback from the testing exercise was used to refine the materials, including updating the content and design of participant information sheets for the main phase.

## 5.5 Other considerations for PPI

### 5.5.1 Designing the Life Study Centres

The Centres will be dedicated Life Study spaces, developed specifically for administering the study interviews and questionnaires and taking measurements, observations and some biological samples. It is important that the centres are not only physically equipped to allow for this, but also designed around the needs of participants. With this in mind, the Life Study team undertook a study centre floor mapping exercise involving participant representatives in a 'virtual walk-through' to collect their feedback on aspects such as ease of access between rooms, buggy space, and positioning of facilities and walkways. As at the time the study centres were being specifically designed and refurbished, it was not possible at this stage to do a walk-through an existing centre. However, consulting participants at this early pre-building stage and then at each decision-making juncture, will be crucial to ensuring that the centres meet participant needs.

### 5.5.2 Local centre-focused PPI, launch of dedicated PPI groups and community engagement

The Pregnancy Component will be recruited through dedicated Life Study Centres. Whilst engagement and PPI to date has been with a range of participant representatives from the general population, it is now necessary to focus community engagement and PPI around the study centre locations to foster a sense of shared ownership with those specific

communities. The Life Study team plans to utilise its relationships with hospital NHS Trusts, other local NHS organisations and local authorities, to develop community networks that will support recruitment to dedicated Life Study PPI groups, whilst also drawing on existing fora.

Local user groups will have an ongoing involvement in the study, providing a consistent resource to be able to draw on for feedback in the initial data collection phases. The benefit of establishing dedicated groups is that this allows for knowledge and understanding of the study, as well as the working relationship, to build over time. This is especially important for Life Study as a complex longitudinal project that will require some level of understanding of the study journey. The relationship of the user group members to the study will also mirror the ongoing involvement of study participants over an extended time, enabling group members to provide informed comment relevant to the stage that participants are at in the study.

It is recognised that each study centre site may require slightly different communication and engagement methods and activities to reach the various social and ethnic minority groups within these communities. The local user groups will provide insights into the best ways to implement this activity. The user groups will also become a central point from which other activity (for example focus groups, interviews and online surveys) can be suggested, designed and planned with member input.

Wider local community engagement, including field visits, attendance at community meetings and events, and addressing potential participants through local religious institutions or community centres, will be built on a solid foundation of local PPI.

### 5.5.3 Further focus group research – fathers and partners, hard-to-reach groups

Through involvement feedback to date, Life Study has already identified some specific audiences whose needs require further investigation and understanding.

The Life Study team is currently planning formal programmes of research with these audiences, which include fathers and partners and some hard-to-reach groups, such as young parents and vulnerable parents.

It is likely that these programmes of audience research will take a similar format to previous focus group research but will be tailored to these audiences where necessary. For example, the style of delivery for the groups and the formats by which feedback is gathered may be changed. Some young parents may be more willing to feedback using private fora, one-to-one, or even via online channels.

It is expected that this research will be delivered in the coming months, prior to commencement of recruitment, and that the outputs will have influence elements of the study design related to participant experience, including recruitment channels, the developing design of the study centres, appointment schedules, staff training and participant retention.

### 5.5.4 Increased use of online and social media for engagement and involvement

Social media has the potential to positively impact the breadth and depth of Life Study engagement and involvement. It provides greater flexibility in the ways that the study is able to engage and involve participants and other stakeholder audiences, including via discussion fora, online surveys, comments and the like.

To date Life Study has primarily used online channels as a means of information provision and recruitment promotion in relation to the pilot study. However, with the establishment of local study centres, locally focused PPI groups and community engagement, social media channels will be exploited in a variety of ways to promote engagement and two-way or multi-party exchanges.

Popular pregnancy and young mother websites, such as Netmums and Mumsnet[21] will be utilised, alongside more local and targeted sites (including fora targeting fathers or ethnic minority groups).

## 5.6 Future PPI

Anticipated future public involvement activities might include input into optimal methods for promoting and disseminating information about study impacts to participants, for example in relation to the use of the data resource and its key findings. Life Study will take an active role in publicising key study findings to participants and will draw on the expertise of public involvement experts and groups in order to achieve this. Public involvement input into ethical study management and data access issues has already been considered within the 'Ethics and Information Governance Framework' and will evolve as Life Study enters the main phase, implements the framework's principles and develops its resources.

Members of Life Study will continue to utilise existing links with stakeholders and partners, including INVOLVE, a national advisory group that supports greater public involvement in NHS, public health and social care research for information on linking with the public and the sensitivities surrounding this outreach.

[21] http://www.netmums.com/ and http://www.mumsnet.com/ (respectively)

# 6 Appendices

## 6.1 Appendix 1: 2012 Birth Cohort Study: Call Specification

# A Leadership Team for the 2012 Birth Cohort Study

## CALL SPECIFICATION

### 1. Summary

1.1. The UK has a unique and internationally renowned collection of birth cohort studies spanning over 60 years. With funding from the Government's Large Facilities Capital Fund we now have an exciting opportunity to extend the series with a new study starting around 2012, and to maximise the value of the existing studies through the development of a new resource to facilitate research across the cohorts and with their counterparts in other countries.

1.2. As the first stage in the development of this exciting opportunity, the Economic and Social Research Council (ESRC) and the Medical Research Council (MRC) are seeking bids to establish the Leadership Team for the new UK birth cohort in or around 2012.[22]

1.3. The new study is intended to support innovative research spanning the interface between the biomedical and social sciences. To reflect this interdisciplinary approach, proposals to provide leadership for the new study must provide combinations of skills, knowledge and research experience from across the biomedical and social sciences.

1.4. To effect such combinations of expertise, skills and knowledge, consortia bids are welcomed. In such cases the lead organisation must be clearly identified and plans for the effective and efficient management of the consortium must be specified.

1.5. The new birth cohort study will provide a major resource for the research community, and also for society generally. To realise the full potential of the new UK birth cohort, the data and biological samples it generates need to be well managed, accessible to the research community, augmented through use and reuse and the results of the research to which they contribute widely disseminated.

[22] With ESRC providing the lead for the initiative overall.

1.6. The successful bidder will provide scientific leadership for the study from 1 October 2009 until 31 March 2015. This period will be split into two phases. A preparatory phase will be established via the award of a contract covering the period 1 October 2009 to 31 August 2010. This preparatory phase will allow time for the detailed elaboration of the study design, work plans and management arrangements. Ministerial approval for the release of 'earmarked' funding will be sought by the Councils in Spring 2010. The Leadership Team will assist the Councils with this process. Subject to ministerial approval a main contract will then be issued to the Leadership Team for the period 1 September 2010 to 31 March 2015.

1.7. The preparatory phase will not include any piloting of specific data collection instruments. It will allow time to establish the feasibility of the research design chosen to support the research themes and specific hypotheses that the Leadership Team proposes to pursue.

1.8. During the main contract period a minimum of two data collections/sweeps across the Cohort will be made. Supplementary funding[23] may facilitate further observation of study members.

1.9. The closing date for receipt of bids is **4pm, Tuesday 30 June 2009.**

1.10. **All applicants are expected to submit to** ESRC **Expressions of Interest** by **Friday 22 May 2009**.

## 2. Background

2.1. Birth and other age or event related cohort studies provide important insights into the complex interplay between biological, environmental, social, economic and health related experiences and conditions. By following individuals over long periods of time and with repeated observation, processes of change can be observed. By linking change to antecedent experiences and conditions, including genetic endowments, researchers have made significant progress in identifying causal pathways across the life course. These cohorts are significant research resources for biological and social sciences especially those that take an interdisciplinary perspective.

2.2. While individual birth cohort studies are valuable research resources in their own right, if undertaken at regular intervals and followed over the life course, they provide a rich basic framework

[23] Additional to already being provided by the ESRC and MRC

for long term investigations across different generations and time periods. The UK has an internationally unique and well established series of national birth cohorts, starting with the National Survey of Health and Development in 1946,[24] the National Child Development Study in 1958, the British Cohort Study in 1970 and the Millennium Cohort (2000/01)[25]. Other major birth cohorts include the Avon Longitudinal Study of Parents and Children[26] – a 1991 birth cohort of children from in and around the Bristol area.

2.3. In 2007 the ESRC and the MRC made a bid to the Department for Innovation and Universities Large Facilities Capital Fund (a major source of Government funding for large scale research infrastructures) to develop a Birth Cohort Facility. The bid was stimulated by the development of the National Data Strategy, and in particular the ESRC Strategic Review of Panel and Cohort Studies[27] which recommended that a new cohort study should be established 'in or around 2012' and that cross-cohort collaboration should be facilitated.

## 3. The Birth Cohort Facility

3.1. In July 2008 ESRC and MRC received notification that £28.5 million had been 'earmarked' from the Large Facilities Capital Fund for the Birth Cohort Facility. As noted above, the full release of funding is subject to Ministerial approval in spring 2010 once the full scientific case (the research rationale) and business case have been submitted. The Leadership Team will be expected to work closely with the Research Councils in the first six months to ensure the strongest possible scientific and business cases are developed.

3.2. The proposed Birth Cohort Facility has three main elements. These are:

- a new **Birth Cohort Study** commencing around 2012;
- a new **Cohort Resources Facility**, designed to stimulate research across and between existing major cohort studies, providing common resources for research purposes and assisting with training and development in longitudinal research;
- a **Secure Access** Facility**, providing** research access to sensitive

[24] See http://www.nshd.mrc.ac.uk/
[25] See http://www.cls.ioe.ac.uk/ for details of the 1958, 1970 and Millennium Cohorts.
[26] See http://www.bristol.ac.uk/alspac/

[27] See http://www.esrcsocietytoday.ac.uk/ESRCInfoCentre/Images/Strategic%20Review%20of%20Panel%20 and%20Cohort%20Studies tcm6-18161.pdf

and/or disclosive data whilst ensuring the safekeeping and protection of individual and organisational identities.

3.3. The Wellcome Trust has now joined with the ESRC and the MRC to assist with the development of this important new research infrastructure. The role and participation of these three funding agencies is indicative of the importance that each attaches to the need to create new and innovative interdisciplinary research in the linked areas of health studies, including cognitive and mental development, and social, educational and economic development and outcomes.

3.4. This Call Specification for the Scientific Leadership of the Birth Cohort Study represents the first stage in the programme of work to establish the Birth Cohort Facility. The detailed specification for the Cohort Resources Facility and the Secure Access Facility will be developed and commissioned at a later date.

## 4. The Birth Cohorts Facility (BCF) Development Group

4.1. The specification for the components of the BCF is being undertaken by a multidisci
the new Birth Cohort Study.

4.2. After careful consideration of a number of study design options the BCF Development Group has recommended that the design of this cohort should be informed and determined by the major social and biomedical/public health research questions and hypotheses which the leadership team propose to address. Bidders are invited to identify these research themes and hypotheses and to present innovative and appropriate research designs to address them.

## 5. The preparatory phase

5.1. The ESRC and the MRC recognise that bidders cannot elaborate all aspects of the desig

- a compelling case for the scientific research themes and hypotheses selected within their bid and a justification of the over-arching study design they plan to elaborate;
- the strength and relevance of the interdisciplinary team they have assembled to develop these scientific programmes and to design, develop, undertake and manage the study and subsequent resource, including plans for the management of the team; and,
- an awareness of the complex issues that they will have to

[28] Membership of the Development Group and its Terms of Reference are shown at Annex 1

address, including ethics and
governance, data sharing, data linkage, resource management and public engagement.

5.2. The successful bid will establish the Leadership Team for the study throughout a five and a half year period. An initial contract will cover the first eleven months (the preparatory phase) which will focus upon the methodology of the study. During this phase the Leadership Team will prepare a detailed plan for the design, methodology and development of the study during the following 55 months and will produce the other outputs specified in sections 6.11, 6.12, 8.2, 8.3, 8.4 and 10.1. These outputs will be used by the Research Councils to assist in obtaining ministerial approval for the release of 'earmarked' funds. Bidders must include details within their bids which indicate how this plan and these outputs will be achieved during the preparatory phase.

## 6. Key requirements for leadership of the new Birth Cohort Study

6.1. This section elaborates further the key requirements, qualities and attributes of research leadership that are being sought for the development of the design and implementation of the new Birth Cohort Study.

The qualities and attributes of the Leadership Team

6.2. The new Birth Cohort Study is being developed as a collaborative investment in research and social scientists to research questions which require long term and large scale resources. Birth cohort studies provide an excellent opportunity to establish close interdisciplinary working, following children through vital stages of their early physical and mental development, recording and monitoring changes in their health, home environment, educational progress and other external influences on their development.

6.3. To reflect this aim, the Leadership Team must be structured to provide expertise across relevant disciplines. The structure of the expertise will relate to two primary and complementary factors: the nature of the major research questions that underpin the proposed study design and the need to create a high quality cohort study as an important future scientific resource. The Team Leader is expected to have an outstanding track record in innovative interdisciplinary research and demonstrated management and leadership skills. The Leadership Team must also demonstrate that it has the combination of expertise and knowledge to:

- provide innovative scientific leadership across the range of

appropriate key disciplines required to address the high level research themes and specific hypotheses to be addressed by the study;

- promote the integration of the range of scientific expertise that will be needed throughout the life of the study; and
- develop a sequenced engagement with stakeholders – these will include not only study members and their families and potential research users of the information generated by the study, but also policy makers and interested members of the general public (as the ultimate funders of the study).

Research issues and the basic design of the study

6.4. The Leadership Team should identify and justify the scientific research themes and hypotheses selected within their bid and the over-arching study design they plan to elaborate. Such issues will involve close collaboration between social and biomedical scientists and will inform both the design of the study and the data to be collected from study participants. Examples of such research themes include:

- parenting, child behaviour and risk taking;
- health, wellbeing, diet and body composition;
- development, behaviour and childhood education;
- childhood infections;
- mental health;
- biological and environmental influences on health and development.

These are indicative examples only. It is expected that the proposal to establish the leadership team will have, at its core, a set of themes and related research hypotheses/questions that drive the design, the combination of expertise that is brought to bear on the research proposed and the nature of the data collection[29] instruments. These themes need to be as enduring as possible throughout the lifespan of the study, thus ensuring that a wide range of research areas are addressed.

6.5. The design of the study should reflect both the scientific research themes and hypo
Cohort Resources Facility will inter alia, promote comparability with earlier birth cohorts. This gives rise to a minimum design requirement that the study should contain a national probability sample sufficient to allow national estimates to be obtained and, where possible, to enable comparability with previous cohorts. Those bidding to provide the research leadership must demonstrate that they are capable of meeting this. The specification

[29] References to 'data collection' refer to collection of data of all types.

of such a sample (population to be sampled, size of the national probability sample and sampling strategy) must be included in bids for the leadership of the study.

6.6. Noting that this is a minimum requirement, bidders may wish to propose elaborations of the minimal design, for example, building upon existing longitudinal resources, area or in-depth sub-studies and/or options combined with the above designs. These should be related clearly to the research issues to be studied and should include an analysis of the advantages and disadvantages of the proposed design.

Other design and methodological considerations

6.7. Proposers should consider ways through which they would incorporate methodological innovation into the design of the study, particularly in terms of data collection. Methods of data collection could include the use of record linkage, web-based data collection methods, or the use of objective measurements of, for example, physical activity, geographical location, diet and health (both physical and mental). If the collection of blood or the use of other invasive techniques in cohort children is proposed, this should be justified scientifically and ethically.

6.8. An important element of any long term prospective study is the need to retain interest and participation in the study by participants. Proposals should include evidence of bidders' awareness of how they might address these issues.

6.9. The BCF Development Group considers that there are strong grounds for recruiting the sample (or a large part of it) antenatally but post conception. Bidders should give careful consideration to this, justifying their chose design scientifically, indicating how it might be achieved, and its implications in terms of the timetable for the study.

6.10. In the period up to 31 March 2015, a minimum of two data sweeps of the Cohort members must be made. These sweeps will provide the basic information that the Leadership Team will need to undertake research on the proposed theme(s). The observations may be supplemented with additional information via record linkage. If there are significant scientific reasons for amending the contract end date, this will have to be negotiated with the funders when the main contact is agreed.

International linkages

6.11. There are major benefits to be gained from the analysis of birth cohort data in international collaborative research

efforts. In order to maximise the potential of the new cohort in this respect it is important that the Leadership Team should demonstrate awareness of the design of major new birth cohorts recently launched or soon to become available in other countries. These include the US National Children's Study, the German National Education Panel Study, the French Longitudinal Study of Children, ELFE (Growing up in France), and other contemporaneous studies. During the preparatory phase a plan should be prepared specifying how ties might be established with these cohorts with reference to potential common design elements.

Engagement with stakeholders

6.12. Experience gained from the development of other large national cohort studies (e.g. Biobank, Millennium Cohort, English Longitudinal Study of Ageing) indicates the importance of having an appropriately sequenced engagement with the variety of stakeholders. Given the needs to retain interest and involvement in the study over the participants' lifetime and to foster public support for its broad objectives, considerable efforts must be made to secure such engagement at different levels. Proposals should contain evidence of bidders' awareness of these issues. During the preparatory phase it is expected that the successful bidder will work with the funding agencies to prepare a stakeholder engagement strategy.

## 7. Procurement procedures for subcontracted activities

7.1. The successful bidder will work closely with the ESRC, the MRC and the Wellcome Trust to specify and develop the infrastructure to collect and link data (administrative records, interview data, clinical measurements, etc.) and biological specimens of various types (blood, sputum or other specimens). Wherever possible, these activities should take advantage of existing facilities to achieve the most efficient means for the collection, treatment and long-term storage of data and biological specimens. If necessary, commissioning of sub-contracted activities will have to go through OJEU procedures, further information about which is available through the OJEU website. [30]

7.2. Data collection for the new study will commence in 2012. Bidders will be expected to include a broad timetable for

[30] http://www.ojec.com

activities relating to the collection of data and biological specimens. This will need to include consultation on topic coverage, preferred OJEU route and piloting.

## 8. Deposition of data and samples

8.1. The successful bidder will be expected to work closely with the funders to agree arrangements to share electronic study data and biological specimens, in line with the MRC, ESRC, and Wellcome Trust Common Framework for Governance Arrangements (Annex 3) at the earliest possible date. This is subsequent to any necessary data validation checks, data cleaning operations, sample preparation, physical analyses, etc. Recognising that the complexity of these arrangements will be determined by the nature of the data and specimens collected, paragraphs 8.2 to 8.4 below describe the outputs in this area which will be required during the preparatory phase. Bidders must indicate within their bids their prior experience with, and proposals for, the deposition, storage and sharing of electronic data and biological specimens.

8.2. A range of options is now available to facilitate the sharing of electronic data. These include access via the ESRC/JISC Economic and Social Data Service under an end user licence, access via Special Licence conditions and access through the ESRC Secure Data Service. During the preparatory phase the successful bidder will be expected to prepare a plan for the deposition of electronic data which makes best use of these or similar facilities and is consistent with the funders' policies on data sharing[31].

8.3. Dependent upon their nature, biological samples may require special transport, treatment, processing and long term storage. Arrangements for these aspects must be developed and specified in the preparatory phase. Bidders should demonstrate relevant expertise and track record of specimen archiving in their team.

8.4. During the preparatory phase the successful applicants will also be required to develop, implement and maintain a Security Plan which will be approved by the Councils,

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[31] See http://www.esrcsocietytoday.ac.uk/ESRCInfoCentre/Images/ESRC%20Research%20Funding%20Guid e tcm6-9734.pdf (ESRC) and http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/Datasharinginitiative/Policy/index.htm (MRC).

tested and periodically updated. The Security Plan will cover issues relating to Data Protection legislation, disclosure control methods and the general management and safe-keeping of the electronic data, metadata and biological specimens collected as part of the study.

## 9. Protection of the identity of study participants

9.1. The names and contact details of study participants will be designated as 'protected data' – to be kept separate from all other data deriving from the study and to be used exclusively for the purpose of maintaining contact with study members or for data linkage purposes where these have appropriate ethical and/or legal approval.

9.2. The stewardship role[32] for protection of this information will fall to whichever bodies assume the scientific leadership of the study throughout its lifetime. The successful bidder will be required to agree to accept this responsibility.

## 10. Governance arrangements

10.1. The Medical Research Council, the Economic and Social Research Council and the Wellcome Trust have established a Common Framework for Governance Arrangements for Longitudinal Studies (see Appendix 3). During the preparatory phase successful bidders will be required to work closely with the funders to prepare a plan for the governance arrangements for the study in accordance with this framework.

## 11. Timetable, budgetary information and the commissioning process

11.1. Bids to undertake the scientific leadership of the study must be submitted by **4pm on Tuesday 30 June 2009.** Detailed guidance on the information required as part of the application is provided in the **'Notes for Guidance'** (see para 11.7).

Timetable

11.2. A commissioning timetable is attached at **Annex 2**.

[32] See Annex 3 for definition of 'stewardship' of electronic data.

Budgetary information

11.3. A total of **£28 million** (at 100% fEC) is available to set up the new Cohort Study.[33] This will cover the Leadership Team costs and a minimum of two waves of data collection, and associated costs. As indicated under paragraph 1.6 at present the funds for the BCF are 'earmarked' with full release of funds subject to Ministerial approval in Spring 2010. Therefore the Leadership Team will initially be appointed via the contract for the preparatory phase covering the period 1 October 2009 to 31 August 2010. Subject to Ministerial approval of funds a full contract will then be issued for the period 1 September 2010 to 31 March 2015.

11.4. The time provided by the preparatory phase contract will ensure that on release of funds the study can remain on schedule to commence in 2012 and enable the team to work with the ESRC and MRC to develop the strongest possible scientific and business case for the study. Bidders should note that they will be required to clearly identify the costs requested as part of the preparatory phase contract.

Importance of a Strategic Partnership

11.5. The ESRC and the MRC will expect the host institution to recognise the international importance of the study and demonstrate how that articulates with its own broad research strategy. The Councils view the development of the study as a Strategic Partnership with the host institution(s).

11.6. The ESRC and the MRC will expect the host institution(s) to demonstrate a commitment to that partnership. One way that this can be achieved is by the host institution(s) making an actual contribution to supporting the development of the study, as has been the case with other major activities recently funded by the Council. This contribution could take the form of either Directly Allocated or Directly Incurred costs. Bids should thus indicate the nature of the proposed host institution(s) support so that this can be finalised prior to awarding the contract in October 2009.

[33] This figure of £28 million includes £23 million of funding from the LFCF 'earmarked' funds, and additional funding of £3 million and £2 million from ESRC and MRC respectively. The remaining £5.5 million of LFCF 'earmarked' funds have been reserved for the Cohorts Resources Facility.

Application Procedure

11.7. Full proposals must be submitted to the ESRC by **4pm on Tuesday 30 June 2009.** Applications should be submitted electronically using the UK Research Council's Joint electronic Submission (Je-S)[34] form available on the ESRC website. Hard-copy, faxed or emailed applications will not be accepted. Detailed guidance notes on the procedures for completing the form are available at: http://www.esrcsocietytoday.ac.uk/ESRCInfoCentre/opportunities/current%5Funding%5Fopportunities/ The ESRC expects interested parties to submit **Expressions of Interest** by **Friday 22 May 2009**, although this is not mandatory.

11.8. To assist the ESRC in preparing for peer review, and to gauge the number of proposals that are likely to be received, applicants are required to notify the ESRC of their interest in submitting a proposal under this call, advising us of the proposed Research Organisations involved in the bid. Applicants should also provide a brief summary of their key research themes and hypotheses for the cohort (no more than 200 words). The information provided will not be published and be used for no other purpose without the agreement of the applicant. Expressions of Interest should be emailed to birthcohortproject@esrc.ac.uk by **Friday 22 May 2009**. Expressions of Interest should **not** be submitted through the Je-S System.

11.9. Proposals will be assessed in the first instance by external referees. These will comprise international leaders within relevant scientific disciplines as well as those with expertise in the design, conduct or analysis of longitudinal studies. A specially convened scientific panel with expertise in large scale (social and biomedical) cohorts, will then assess the proposals following which shortlisted candidates will be invited for interview during September 2009.

11.10. Proposals will be assessed by the Commissioning Panel against the following criteria:

- The originality and importance of the scientific research themes and hypotheses proposed.
- The excellence and innovative features of the proposed research and of the study design.

[34] See https://je-s.rcuk.ac.uk/ Please note that organisations wishing to register for Je-S should contact the helpdesk at JeSHelp@rcuk.ac.uk Tel: 01793 444164 (open 9am to 5pm weekdays, except holidays). Users wishing to access the Je-S system for the first time are asked to check with their central administration on the status of the organisation's Je-S registration before pursuing the option of creating an account through the Je-S system.

- The intellectual, leadership and management skills of the Team Leader.
- The capability and experience of the team to carry out the work, including scientific and stakeholder engagement skills.
- Understanding of the requirements (as specified above).
- The feasibility of the proposed project management plan.
- Costs and value for money (the ESRC and the MRC are not bound to accept the lowest bid).

11.11. The recommendation of the Commissioning Panel will be considered by the ESRC Research Resources Board and the MRC Strategy Board in September 2009.

11.12. It is anticipated that the initial contract for the Study will be from **1 October 2009 until 31 August 2010.** Subject to ministerial approval, a full contract will then be issued from for the period September 2010 to 31 March 2015. During this time a mid-term review will take place where consideration will be given to any renewal of the award. It is anticipated that the review will take place in order to allow sufficient time for the decisions to be made regarding the funding of future data collection activities.

11.13. Any enquiries relating to the initiative or to ESRC research funding rules should be addressed in the first instance to:

Dr Esther Wilkinson
Telephone: 01793 413152
Email: Esther.Wilkinson@esrc.ac.uk

or Mr Luke Moody
Telephone: 01793 444520 Email: Luke.Moody@esrc.ac.uk

11.14. Any enquiries relating to the Je-S application procedure should be addressed to the Je-S helpdesk at: Tel: 01793 444 164
Email: Je-Shelp@rcuk.ac.uk

11.15. Applicants should note that any attempt to lobby ESRC or MRC Officers, Peer Reviewers, and members of the Development Group, ESRC Research Resources Board or Council will result in immediate disqualification of the application concerned.

# A Leadership Team for the 2012 Birth Cohort

# Study CALL SPECIFICATION

## Annex 1: Birth Cohort Facility Development Group Terms of Reference and Membership

### Terms of Reference

1. The BCF Development Group is appointed by the ESRC Research Resources Board to oversee the development of the project to implement the new Birth Cohort Facility.

2. The Terms of Reference for the Group are:

- to advise on the development of the Strategic Outline Business Case and Full Scientific Case;
- to develop the specification for the scientific teams for both the cohort facility and the 2012 cohort study;
- to advise the Research Resources Board on scientific issues regarding the appointment of the cohort facility team, and both the 2012 cohort study scientific and data collection teams;
- to provide guidance to the Research Resources Board on necessary stakeholder, user and public consultation and engagement;
- to consider the impact of the BCF on both existing birth cohort studies, and the wider portfolio of current resource investments;
- to consider lessons learnt from the Understanding Society project.

### Membership

3 Membership of the BCF Development Group is detailed below. This draws its expertise from various academic and 'user' stakeholders.

**Professor Peter Elias** (Chair), ESRC Strategic Advisor (Data Resources), University of Warwick

**Professor James Nazroo** ESRC Research Resources Board, University of Manchester

**Professor Maria Evandrou** ESRC Research Resources Board, University of Southampton

**Professor John Hobcraft** University of York

**Professor Carol Dezateux** MRC Centre of Epidemiology for Child Health, Institute of Child Health, University College London

**Professor Cyrus Cooper** MRC Epidemiology Resource Centre, University of Southampton

**Dr Pat Goodwin** Wellcome Trust

**Mr Paul Allin** Office of National Statistics

**Dr Angela Cooper** Medical Research Council

**Mr Matthew Sowemimo,** ESRC Director of Communications for Longitudinal Studies

# A Leadership Team for the 2012 Birth Cohort Study CALL

# SPECIFICATION

**Annex 2: Commissioning Timetable**

| Date | Activity |
|---|---|
| April 2009 | Bidders Workshop, Thursday 30 April 2009 (12.30pm to 4.15pm) in London. |
| June 2009 | **Closing date for applications for PI team 4.00pm Tuesday 30 June 2009** |
| July 2009 | Peer Review of applications |
| September 2009 | **Commissioning Panel Meeting**<br><br>**Interviews with shortlisted applicants, week commencing 07 September 2009**<br><br>**ESRC Research Resources Board and MRC Strategy Board agrees PI team** |
| October 2009 | Contract(s) finalised for PI team (to start 1 October 2009) |
| November 2009 - December 2011 | Ministerial approval of Full Business Case<br><br>Finalisation of main contract Scientific Leadership Team for cohort study.<br><br>Finalise fieldwork<br><br>arrangements. Design and<br><br>pilot study |
| From April 2012 | **Full Study enters the field.** |

# A Leadership Team for the 2012 Birth Cohort Study CALL

# SPECIFICATION

## Annex 3: Framework for Governance Arrangements for Longitudinal Cohort Studies

### 1 Introduction

Longitudinal cohort studies created through public and charitable funding, and with the benefit of public and patient participation, are resources of major importance for biomedical, health-related and social scientific research. The funders expect that they should be governed, managed and used so as to maximise public benefit.

To realise the full potential of these studies as research resources, they need to be well managed, accessible to the research community, augmented through use and re-use and the results of the research to which they contribute widely disseminated.

Two major considerations have a bearing on the use and accessibility of these resources for research - the rights and interests of the research participants (which need to be safeguarded, in accordance with legal, regulatory and ethical requirements), and the depletability of the biological samples (which necessitate a method for rationing). Governance arrangements should be designed to address these considerations.

Although the detailed governance arrangements will vary, depending on the nature of the study, the circumstances of their establishment, their location and the data and samples collected, there are many common issues, and certain principles and procedures that should be reflected across all studies. This Framework gives guidance on those common issues, and on the principles and procedures that should be reflected in the arrangements for the management and use of individual studies.

### 2 Stewardship

Good stewardship of each study is critical to the achievement of its full potential as a research resource. There are a number of aspects to this, including in particular:

#### 2.1 Ensuring that use/ access is suitably managed and use maximised.

Responsibilities include:

a. devising, articulating and implementing suitable processes for handling use/ access;
b. facilitating and supporting use of the resource;
c. processing and deciding on requests for access;
d. ensuring that access/ use is granted in conformity with legal and ethical

requirements and the participants' consent;
e. policing compliance with terms of access and pursuing infringements.

**2.2 Ensuring the resource is well managed, curated and developed/ enriched.**

This will include:

a. protecting, preserving, managing, promoting and enriching the resource;
b. sample and data management and handling/ archiving;
c. maintaining sample and data security and confidentiality;
d. seeking and managing core funding and business plans/ charging strategy to ensure sustainability;
e. managing property (in samples) and intellectual property rights in the resource;
f. handling and implementing access requests;
g. collecting/ handling new data and samples.

**2.3 Managing the relationship with the research participants**, their rights and interests and any risk of harm – this includes fulfilling any commitments made to them at recruitment (e.g. during the consent process) and at other times, and complying with relevant legal, regulatory and ethical requirements.

Responsibilities in this regard include:

a. managing contact with participants on enrolment, recruitment, follow up and at other stages;
b. seeking consent from participants (and any further consent as necessary);
c. ensuring compliance with all legal, regulatory and ethical requirements relating to participants (including responsibility to relevant regulators), and conformance with participants' consents;
d. handling issues relating to feedback of individual or general results to participants;
e. handling issues relating to withdrawal of consent;
f. handling complaints/ adverse incidents;
g. addressing new legal or ethical issues arising in the course of the study.

The institution and staff responsible for stewardship should be clearly identified and have the ability to carry out their responsibilities in full. Management and governance responsibilities within that should be clearly delineated. Given the importance that attaches to these responsibilities, it may be appropriate to establish a Stewardship Board with executive powers and Terms of Reference that reflect the duties it must conduct.

The various responsibilities associated with stewardship may be shared between several institutions, or delegated or assigned to a separate body, provided this is consistent with legal and regulatory requirements and that participants remain clear about the arrangements, and how and by whom their interests are being safeguarded. The carrying out of these responsibilities may be subject to independent oversight, either through existing regulatory mechanisms (e.g. the NHS Research Ethics Committee) or a special mechanism created for the study (e.g. the UK Biobank Ethics and Governance Council).

**3 Access management**

Arrangements for access should be designed to ensure that research use is permitted as rapidly and widely as possible so as to maximise public benefit from the resource, with due regard to the legal and moral responsibilities of the study to the research participants.

### 3.1 Mechanisms for access/ data sharing

Depending on the range and sensitivity of the data and samples collected, a suite of mechanisms to share data and provide access may be appropriate to ensure that access is maximised. Any controls applied should be proportionate to potential risks, should not create unnecessary barriers to research and the various routes for access clearly explained.

Access to samples or to participant-related data that carry a risk of direct or indirect disclosure of personal information will require the highest degree of management and control, with the samples and data only being accessible by application. The materials may then be provided directly to the researchers, possibly in limited amounts (to reduce the disclosure risk), under the control of an access agreement, or via a safe setting. Less sensitive data, particularly non-disclosive datasets, may be suitable for sharing more openly, for example, through limited access websites with secondary controls, or on openly accessible websites.

### 3.2 Procedures for managing access

General requirements

Procedures for access to and use of the resource should be clearly articulated to participants and potential users. All access to and use of the resource for research, including by the investigators involved in creating the resource, should be governed by those procedures.

Access to the resource should be open to all researchers on a non-exclusive basis, for the research purposes for which the study was established, within the terms of the participants' consents. Access procedures should be fair, open and transparent and not unnecessarily obstruct or delay research use of the resource.

Procedures may differ for access to different parts of the resource (e.g. access to data repositories versus access to samples), to different types of data (e.g. data that is highly disclosive versus fully anonymised data; raw versus augmented data), or to link data (e.g. phenotype to genotype). In particular, the level of scrutiny and independent review may vary according to the level of risk/ sensitivity. In each case, procedures should be proportionate to the risks and sensitivities associated with the materials concerned. Co-ordination across mechanisms to ensure consistency between parts of the resource will be essential.

Application process for managed access

The development of access applications should be facilitated and encouraged through the provision of information promoting the resource and highlighting the data and samples available, either openly, by application, or otherwise.

Any application for access to data or samples should be accompanied by a clear statement of the proposed research use and should include sufficient information to

enable the steward of the resource to establish that the material requested is relevant to and appropriate for that purpose.

Where not separately undertaken (e.g. as part of the funding process), independent scientific review and ethical approval of applications to use samples or data may be required and consideration should be given to the needs for this as part of the access application process.

### Decision-making

Responsibility and authority for decision-making ultimately rests with the steward of the resource. This may be delegated or assigned to a particular group or body, or in some cases, an individual, provided it is clear where the responsibility and authority in any particular case lies and the decision-makers are accountable for their decisions. Care should be taken to avoid separating responsibility and authority.

Decision-making processes should be clear, transparent and timely. They should involve the provision of expert advice where necessary. They should also include mechanisms for managing conflicts of interest.

### Independent involvement in decision-making

In many cases, and particularly for large national resources, independent involvement in decision-making may be necessary:

a. To manage conflicts of interest, or
b. To represent or speak from the perspective of the participants.

This could involve the inclusion of independent voice(s) in a Stewardship Board, or some form of independent review mechanism. This should be clearly articulated in the decision-making structure and in the terms of reference of any bodies including such independent input.

### Criteria

Criteria for access, including eligibility criteria and criteria for prioritisation of access to depletable samples, should be transparent and objective, and designed to maximise the research value of the resource for public good.

### Referral

Instances may arise where, for various reasons, an application to access data or samples is rejected. In the vast majority of cases, the grounds for refusal will be clear, justifiable and acceptable to the applicant. To address the unlikely situation where this is not the case, the steward should consider implementing mechanisms to resolve disputes to the satisfaction of all parties. This may involve utilising internal escalation procedures in the first instance. This should be explicitly defined. Rarely, situations may arise where there is an unresolved tension, for example, between the scientific value of the proposed research use and the participants' interests. Such cases may be referred to the funders who may seek expert advice or review in determining a potential solution.

### Implementation

Once an access application has been granted, the request should be processed promptly.

Requests may need to be prioritised if they are numerous and resources are constrained.

### 3.3 Terms of access

De-identification prior to release

Data and samples will only be available for use within the participants' consents. The consents may limit use of the data and samples to use in anonymised form. Even where this is not the case, the risk of disclosure of participants' identities to researchers should be avoided, except where this is necessary and justified in the access application, to minimise the risk of harm. This will generally mean that data and samples should be de-identified as far as possible prior to release. Researchers who gain access to resources also have a responsibility to ensure they do not attempt to identify individuals (outside the agreed purposes of their research) or claim to have done so.

Access agreements

The user and, in some circumstances his/ her institution, should be asked to sign a licence agreement and/ or a material transfer agreement with the steward of the resource. These agreements should set out the terms of access. The steward of the resource may need to police compliance with these agreements and consider applying sanctions in the event of breach, or misuse of data and samples. Issues of non-compliance that cannot be resolved between the parties may be referred to the funders for consideration.

Specification of access agreements

Access agreements are likely to specify some or all of the following terms and conditions:

- the researcher(s) and their institution(s) authorised to use the materials;
- details (and a delimitation of) the purpose for which the data and samples may be used;
- details of the ownership of research results;
- obligations concerning the dissemination and publication of research results and return of data/ samples to the resource;
- licence fees, if applicable;
- duties of confidentiality including undertakings to ensure that participant anonymity is maintained;
- limits or prohibitions on onward transfer of data or samples;
- limits or prohibitions on the linking of data with other data or samples;
- prohibition on recontacting research participants;
- (for transnational access) additional protections concerning foreign legal jurisdictions;
- details of any requirement concerning the acknowledgement of the use of the resource;
- details of any conditions for data/sample transfer, management, storage or security
- other requirements necessary to ensure compliance with the responsibilities of the resource to the participants (which, depending on the arrangements with participants, could include obligations in relation to individual health deriving from data or samples, obligations in the event of withdrawal of consent and

compliance with any other terms of the consents);
- details of any ethical requirements;
- standard legal disclaimers regarding quality/ errors and
- provision for the consequences of any breach.

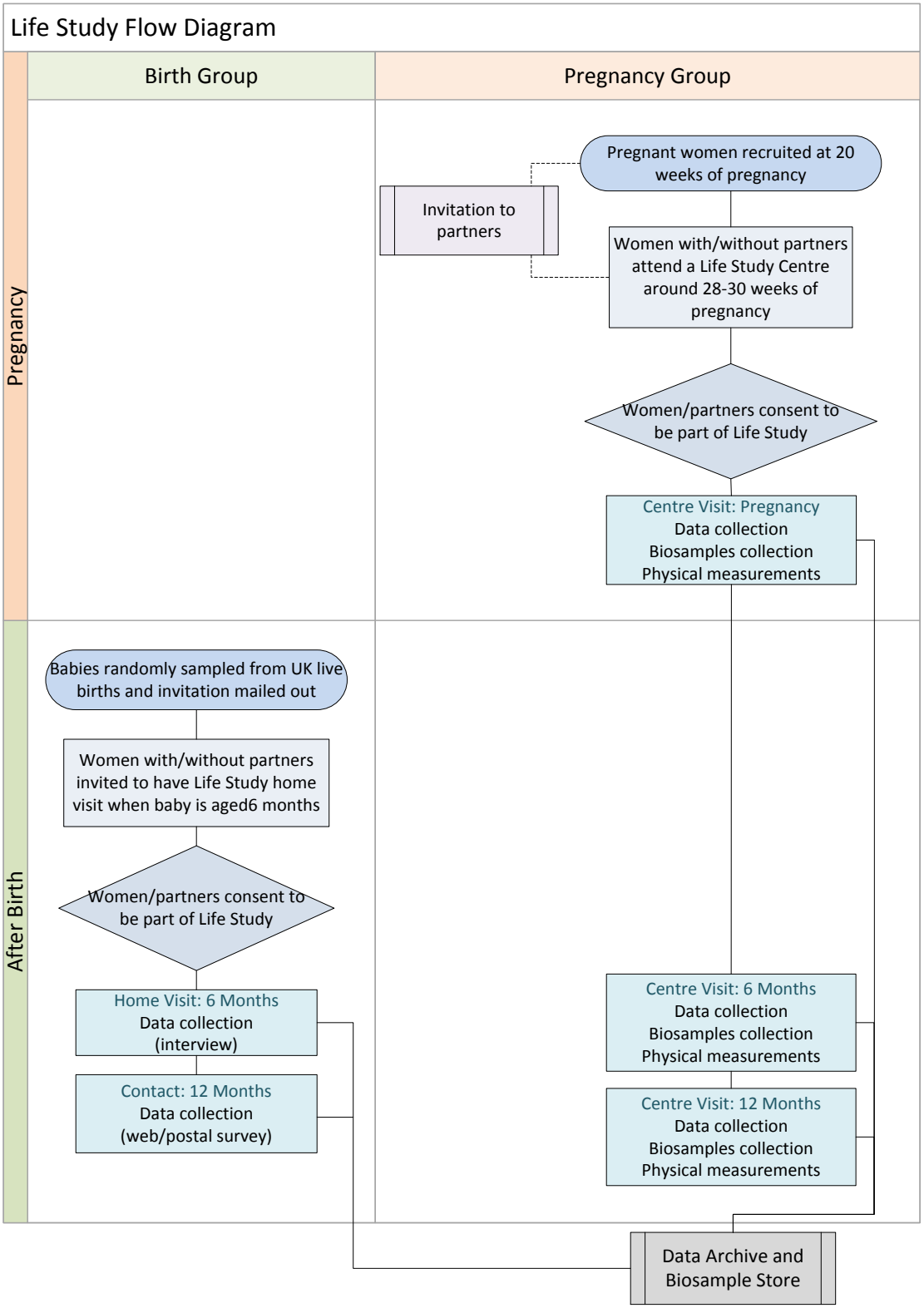
Exclusivity

Access to data and samples should not be granted exclusively, though the sharing of research results may be delayed in certain circumstances for short periods to allow researchers to publish their findings or seek patent protection.

Generally, no preferential access should be given to those involved in the creation of the study, on the basis that the purpose of creating the study is to develop a resource for the whole research community, to which access will be granted openly, or controlled and prioritised on the basis of scientific merit. Those involved in the creation will of course be particularly well placed to gain access on the basis of scientific merit alone.

However, there may be situations where a study is created, or a new sweep conducted, for the primary purpose of testing specific hypotheses. In these situations, the funders may consider allowing the investigators concerned a reasonable delay before sharing the data and materials more widely in order to fulfil the study's (or the sweep's) primary purpose. This will need to have been considered as part of the original funding proposal.

## 6.2 Appendix 2: Flow Diagram of Life Study



## 6.3 Appendix 3: Sample Size and Sampling Methodology

### 6.3.1 Summary of conclusions on sample size and statistical power presented in original scientific case

A full technical report of the Life Study power calculations was presented for the 2009 bid. This was reviewed in 2013 when further information on sample size was discussed by the SSC and ISAC and then presented to the Life Study Corporate Board in June 2013 (LSCB 13/1 Annex 3). This informed the funders' approval to release funds for the Innovation Phase (Phase 1) and were part of the Life Study Business Case version 12.3.

Scientific progress on the five research Life Study themes demands that there is sufficient power to enable reliable detection of moderately strong causal effects of risk factors (environmental, psychosocial, genetic) that are moderately common (e.g. prevalence ≥ 10%) on outcomes that are other than rare (e.g. prevalence ≥0.5%).

Such outcomes include: asthma (>5%); ADHD [DSM IV] (4%); strabismus (2%); and idiopathic epilepsy (0.5%). The calculations demonstrate these criteria to be satisfied by 100,000 recruits but not 50,000.

A sample size of 100,000 subjects provides adequate power to detect associations between determinants of modest or large effect and binary traits that are present in the cohort with a prevalence of at least 1%.

A sample size of 100,000 recruits provides excellent power for quantitative traits. The power of such traits will also be of central importance to the analysis of key traits within and between ethnic groups which is fundamental to our overall research program. Our sampling model will ensure sufficient participants in 3 ethnic groups (White European, South Asian and Black) for analysing quantitative traits, but there will also be sufficient power for some binary traits

The Life Study is an effective platform for genome wide association or sequencing studies particularly when they are based on quantitative traits.

A sample size of 100,000 is appropriate for the full cohort. In coming to this conclusion, it is noted that the apparent requirement could be reduced by ignoring the relevant bio-analytic complexity that is taken into appropriate account in our calculations. Ignoring realistic levels of such complexity can easily halve the apparent sample size requirement. But evidence from the genomics world suggests that if studies are designed with unrealistically small sample sizes, real effects are hard to detect and most reported effects are false positives. This is seriously detrimental to the advancement of biomedical science.

The US National Children's Study (NCS) also viewed case-control analyses based as being a key determinant of statistical power and also selected a sample size of 100,000. Taking full account of differences in the two sets of assumptions, our estimates of statistical power are more conservative than theirs but the difference is relatively small. The sample size

calculations from the December 2012 US NCS 'White Paper' have been reviewed and in brief demonstrate, albeit more conservatively than the Life Study calculations, the statistical power expressed for different disease outcomes. The frequency of these outcomes is mostly comparable with those estimated for the UK.

**Key results of Life Study power calculations from 2009:**

Table S1: Environmental Main Effects

Statistical power (at p<0.01) to detect a relative risk of the size stated with 100,000 subjects

| Prevalence of disease | 5% | 2% | 1% | 0.5% |
|---|---|---|---|---|
| Relative risk* | | | | |
| 1.5 | 0.5** =>99%<br>0.2** =>99%<br>0.1** = 88% | 0.5** = 96%<br>0.2** = 74%<br>0.1** = 42% | 0.5** = 68%<br>0.2** = 38%<br>0.1** = 19% | 0.5** = 34%<br>0.2** = 17%<br>0.1** = 8% |
| 1.67 | 0.5** =>99%<br>0.2** =>99%<br>0.1** = 98% | 0.5** =>99%<br>0.2** = 97%<br>0.1** = 63% | 0.5** = 88%<br>0.2** = 71%<br>0.1** = 30% | 0.5** = 53%<br>0.2** = 36%<br>0.1** = 13% |
| 2.00 | 0.5** =>99%<br>0.2** =>99%<br>0.1** =>99% | 0.5** =>99%<br>0.2** =>99%<br>0.1** = 93% | 0.5** =>99%<br>0.2** = 95%<br>0.1** = 62% | 0.5** = 82%<br>0.2** = 67%<br>0.1** = 30% |

*Relative risk associated with "at risk" environmental exposure v "not at risk"
**Prevalence of "at risk" environmental exposure

Table S2: Genetic Main Effects

Statistical power (at p<10-4) to detect a relative risk of the size stated with 100,000 subjects

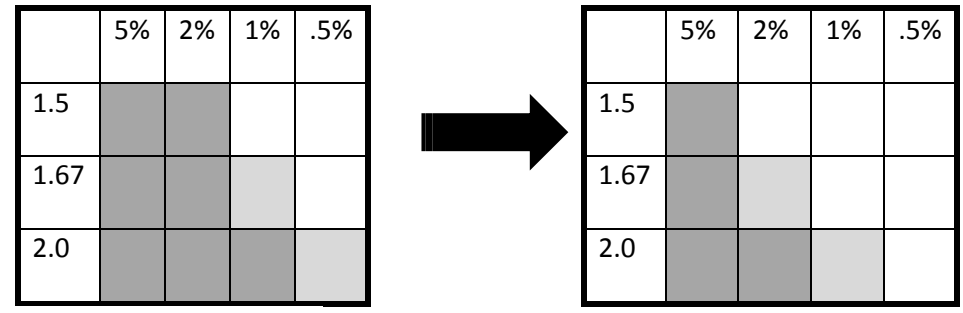
| Prevalence of disease | 5% | 2% | 1% | 0.5% |
|---|---|---|---|---|
| Relative risk* | | | | |
| 1.5 | 0.3** =>99%<br>0.1** =>99%<br>0.05** = 98% | 0.3** =>99%<br>0.1** = 87%<br>0.05** = 46% | 0.3** = 94%<br>0.1** = 37%<br>0.05** = 11% | 0.3** = 49%<br>0.1** = 8%<br>0.05** = 2% |
| 1.67 | 0.3** =>99%<br>0.1** =>99%<br>0.05**=>99% | 0.3** =>99%<br>0.1** =>99%<br>0.05** =89% | 0.3** =>99%<br>0.1** = 77%<br>0.05** = 39% | 0.3** = 84%<br>0.1** = 27%<br>0.05**= 9% |
| 2.00 | 0.3** =>99%<br>0.1** =>99%<br>0.05**=>99% | 0.3** =>99%<br>0.1** =>99%<br>0.05**=>99% | 0.3** =>99%<br>0.1** =>99%<br>0.05**=>85% | 0.3** =>99%<br>0.1** = 77%<br>0.05**= 34% |

*Allelic relative risk under additive genetic model
**Minor allele frequency (MAF)

Tables S1 and S2 indicate that a sample size of 100,000 subjects provides adequate power to detect associations between determinants of modest or large effect and binary traits that are present in the cohort with a prevalence of at least 1%. Furthermore, if the trait

prevalence is as low as 0.5% there is still acceptable power for meaningful analysis if the exposure prevalence is high or the relative risk is large. Rarer determinants of small magnitude affecting rarer traits (≤0.5%) demand pooled collaborative analysis with harmonized cohorts to achieve adequate statistical power.

Figure S1




100,000 recruits

50,000 recruits

Using the same shading as tables S1 and S2, figure S1 provides a schematic representation of the fall in statistical power obtained (for both the environmental and the genetic effect if the overall sample size is reduced to 50,000 recruits.

### 6.3.2 Summary of conclusions on sample size and statistical power prepared in June 2013

In mid-2013 Professor Burton replicated the sample size calculations carried out in mid-2009 using the same methodology and a wider range of sample sizes from which Francesco Sera the Life Study survey statistician compiled the following power curves.

Professor Carol Dezateux compiled the outcome and exposure data using UK estimates. The following tables and graphs summarise the findings.

The power curves presented give – firstly, curves for environmental main effects for a range of outcome prevalences (10%, 5%, 2%) and two exposure prevalences (10% and 20%); and secondly, for the genetic main effects using two allele frequencies (5% and 30%) for the same outcome prevalences.

In summary under the extreme considerations represented in these analyses (binary outcomes and binary exposures) power is preserved for all but environmental main effects at 2% outcome prevalence for a sample size of 50-60,000 in the Pregnancy Component.

A further written commentary by Professor Burton was considered:

“Looking over the revised power profile, the results demonstrate that data on 50,000 participants will provide acceptable power to study the key classes of question that you

wish to study. In saying this, however, it is important to recognise that 50,000 original recruits never translate into 50,000 usable participants for any particular analysis. In consequence I'd tentatively suggest that you probably ought to aim for 60,000 initial recruits on the basis that this will provide you with at least 50,000 subjects with complete data for many things you'll then study.

Although the power for environmental determinants on rare (<2% prevalence) phenotypes (e.g. neurological conditions) may appear to be limited (odds ratios need to be close to 2.0 to get power up near 80%), many non-genetic factors considered to be of epidemiological interest are associated with large odds ratios. This is not least because, unlike genetic variants, they are not protected by Mendelian Randomisation and so small odds ratios are rather difficult to interpret anyway.

For the purposes of the power calculations, non-genetic determinants have been modelled as binary whereas in reality more and more non-genetic factors are being measured as continuous variables. This includes, for example, quantitative measurements of biomarkers and these are in general considerably more powerful than binary measures. The increasing use of high throughput multi-endpoint biomarkers is one of the most important reflections of our enhanced capacity to measure not only the state of health of individual participants but also their environmental exposures. In the same way many measures of the wider environment (e.g. pollution) are naturally quantitative in nature, as too are many of the key scales and measures in psycho-social science.

Consequently, I am confident that the power profiles for binary non-genetic determinants underpin what will actually be a very healthy capacity to study quantitative environmental determinants as they become increasingly available, and also gene-environment interactions."

## Table S3: Outcome and exposure prevalences expected in UK children in early childhood

| Outcome | Definition | Age (years) | Prevalence of outcome (%) | Expected n per 50,000 | Source |
|---|---|---|---|---|---|
| Preterm birth[1] | < 37 weeks gestation | 0 | 6% | 3000 | Moser et al 2005 |
| Asthma phenotypes[2] | Parental report/doctor diagnosed asthma | 3 years | 11.7% | 5850 | MCS |
| Obesity[4] | BMI obese | 3 years | 5% | 2500 | MCS |
| | | 5 years | 5% | 2500 | MCS |
| Overweight[3] | BMI overweight | 3 years | 18% | 9000 | MCS |
| Longstanding illness[4] | Parental report | 3 years | 15.8% | 7900 | MCS |
| Recurrent ear infections[5] | Parental report | 3 years | 6.5% | 3250 | MCS |
| Autism spectrum disorders[5] | Parental report of doctor diagnosed | 7 years | 1.7% | 850 | MCS |
| Learning disabilities[6] | Special educational needs with statement | 7 years | 2% | 1000 | English school administrative data[6] |
| Exposure | Definition | Timing | Prevalence of exposure | Expected n per 50,000 | Source |
| Tobacco use in pregnancy | Smoked before or during pregnancy | Pregnancy | 26% | 13000 | Infant Feeding[7] Survey 2010 |
| | Smoked throughout pregnancy | Pregnancy | 12% | 6000 | Infant Feeding[7] Survey 2010 |
| Maternal alcohol consumption | >3 times a week | child age 9 months | 15.7% | 7850 | MCS[8] |

[1] Moser et al Health Stat Q. 2008 Autumn; (39):22-31, 34-55.
[2] Henderson et al Thorax 2008; 63: 974–980. doi:10.1136/thx.2007.093187
[3] Griffiths LJ et al Int J Pediatr Obes. 2011 Jun;6(2-2):e423-3
[4] Millennium Cohort Study 2nd Survey: A User's Guide to Initial Findings; Hansen, Joshi 2007
[5] Russell J Autism Dev Disord. 2013 May 30. [Epub ahead of print]
[6] Meschi, Micklewright, Vignoles & Lindsay DfE research report DFE-RR247-BCRP11 published December 2012
[7] Infant Feeding Survey 2010: Early Results NHS Information Centre 2011
[8] Millennium Cohort Study 1st Survey: A User's Guide to Initial Findings; Dex, Joshi 2004

Figure S2: Power curve environmental main effects: outcome 10% exposure 10%

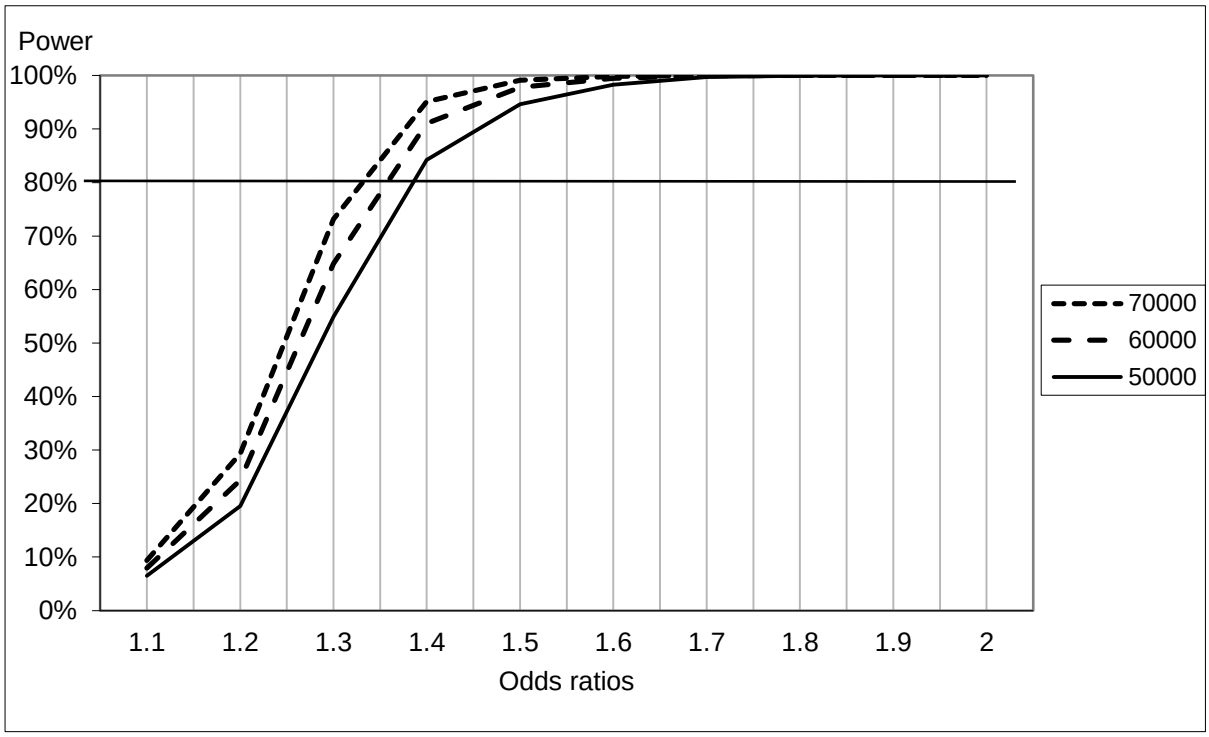



Figure S3: Power curve environmental main effects: outcome 5% exposure 10%

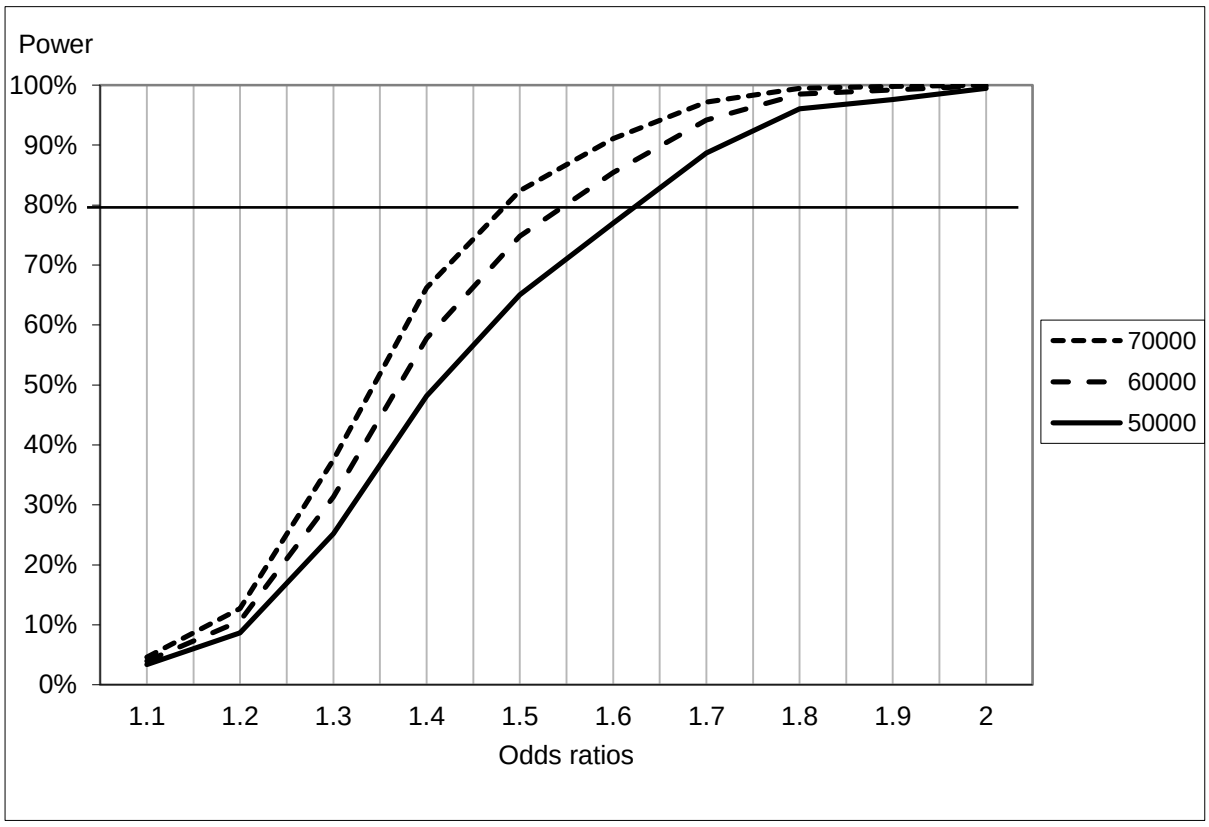


Figure S4: Power curve environmental main effects: outcome 2% exposure 10%

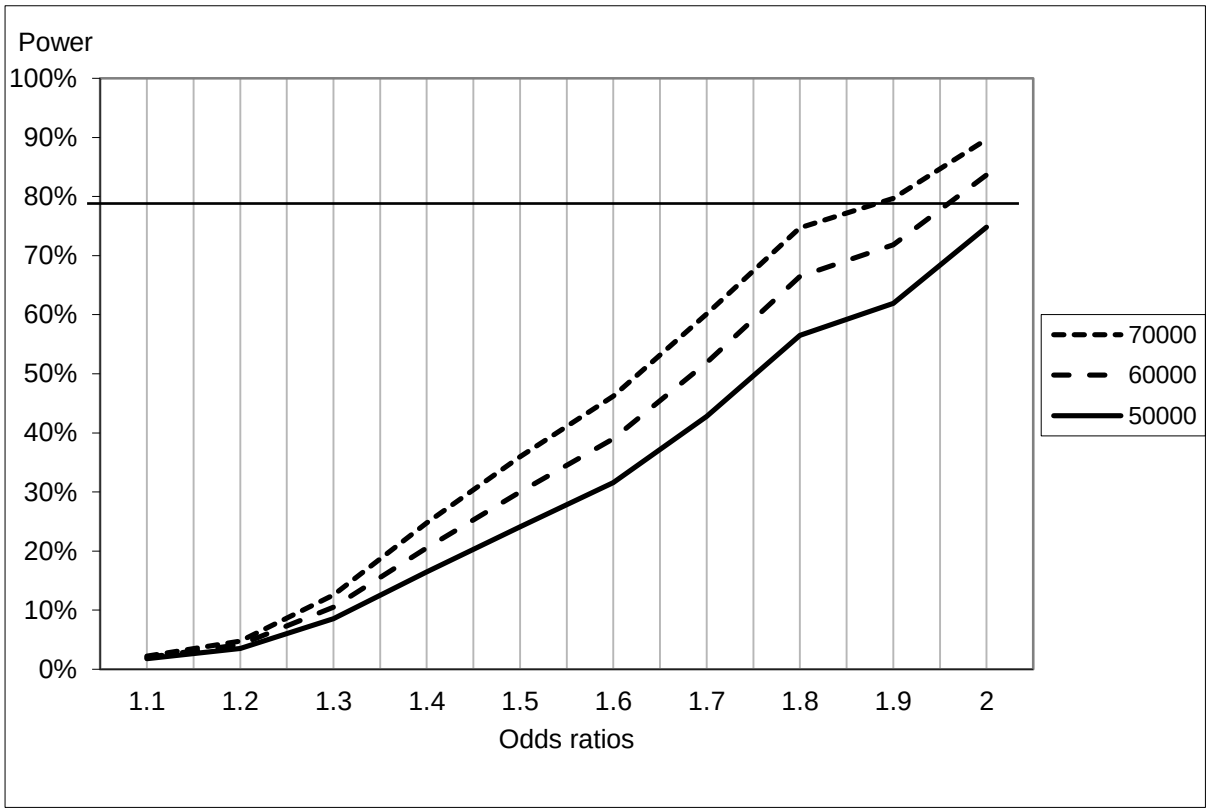



Figure S5: Power curve environmental main effects: outcome 10% exposure 20%

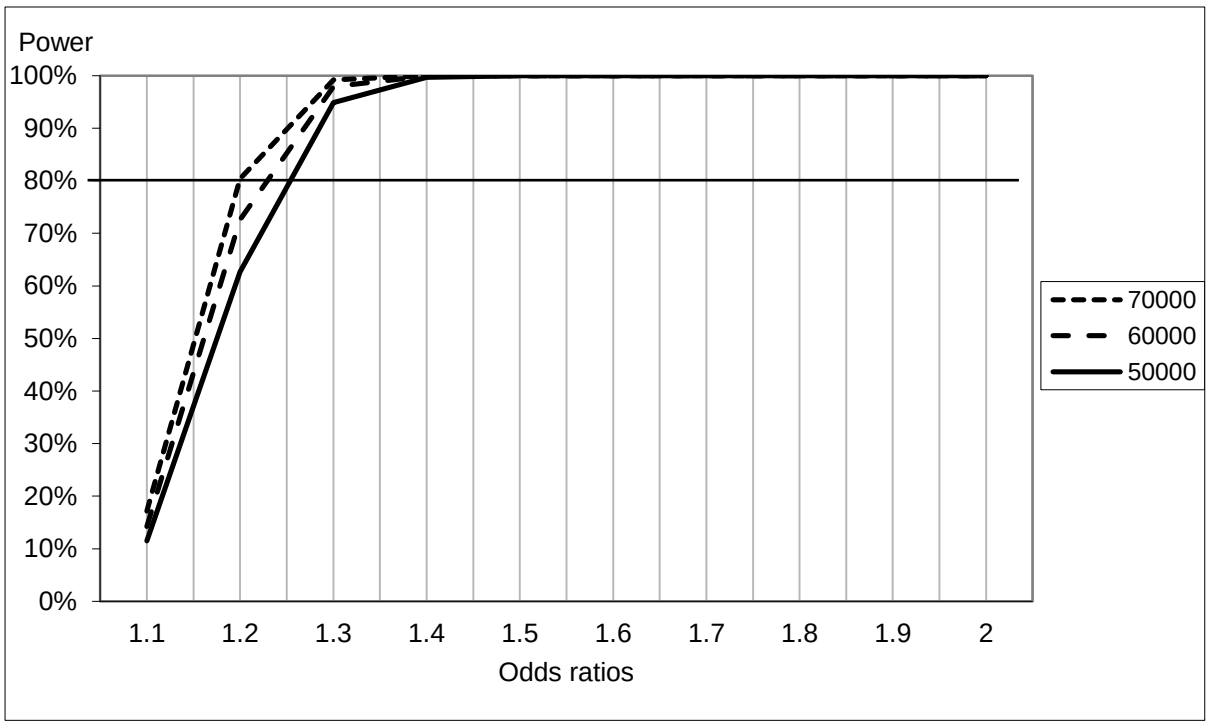


Figure S6: Power curve environmental main effects: outcome 5% exposure 20%

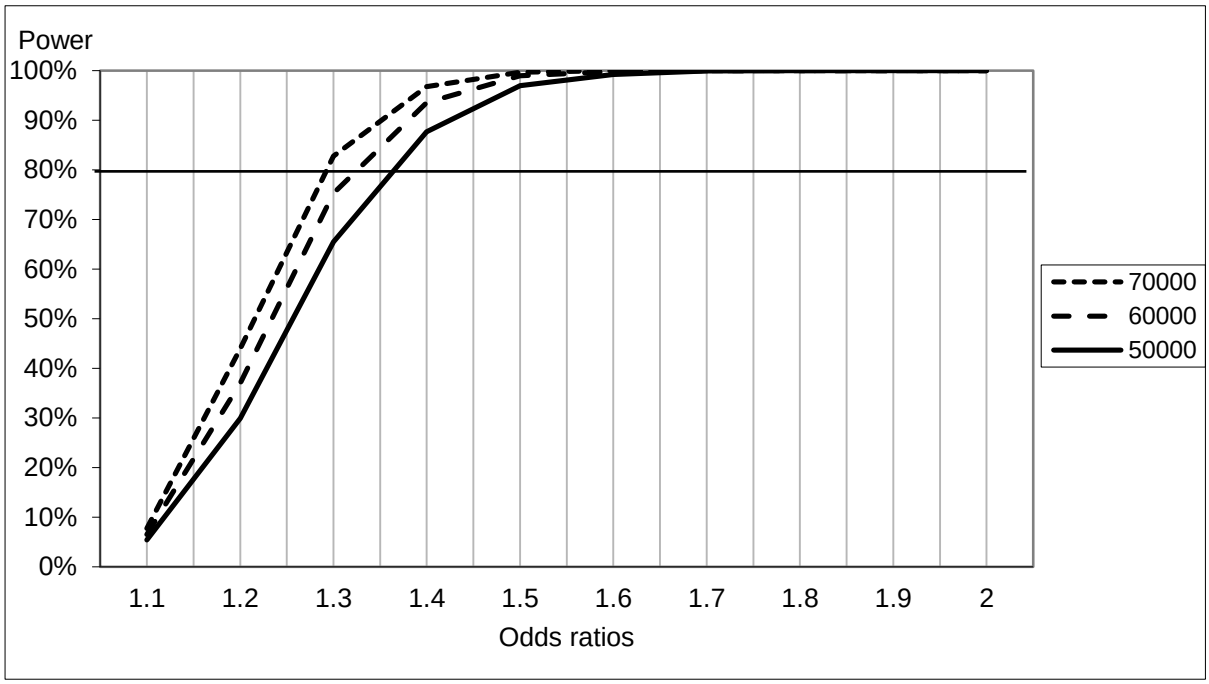



Figure S7: Power curve environmental main effects: outcome 2% exposure 20%

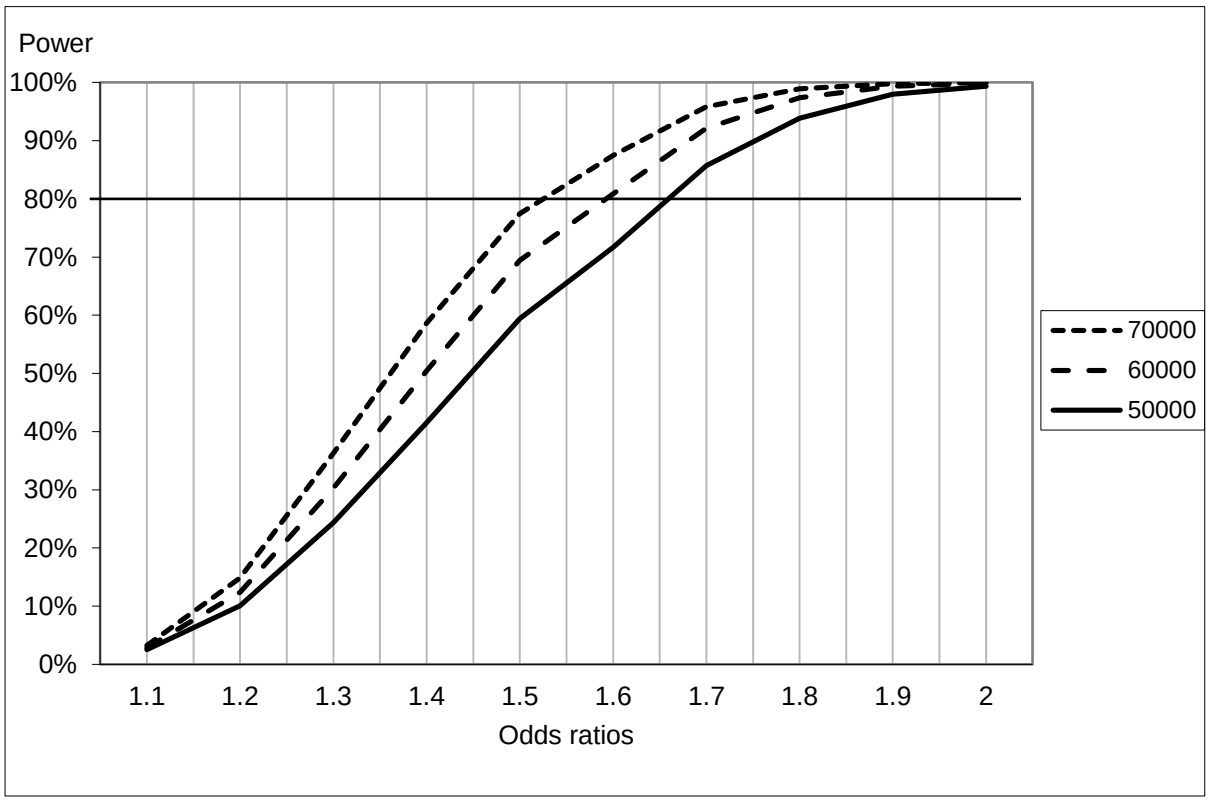


Figure S8: Power curve genetic main effects: outcome 5% MAF 30%

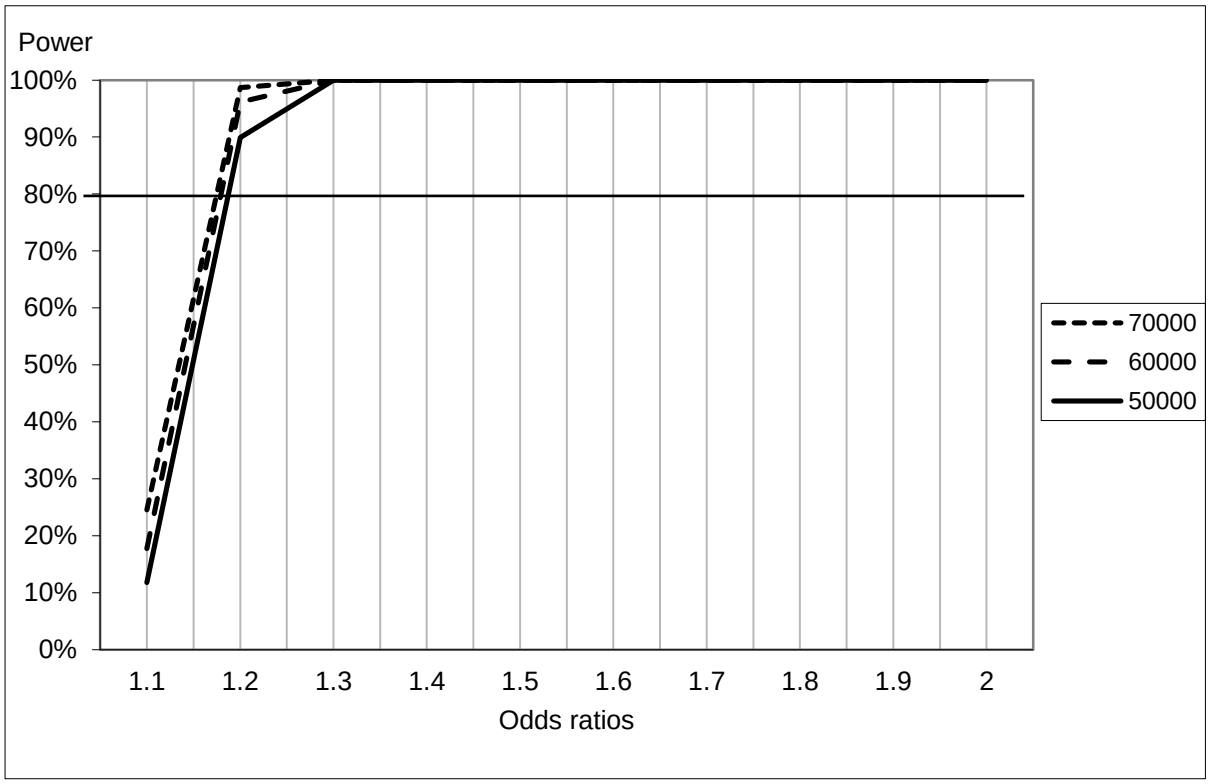



Figure S9: Power curve genetic main effects: outcome 2% MAF 30%

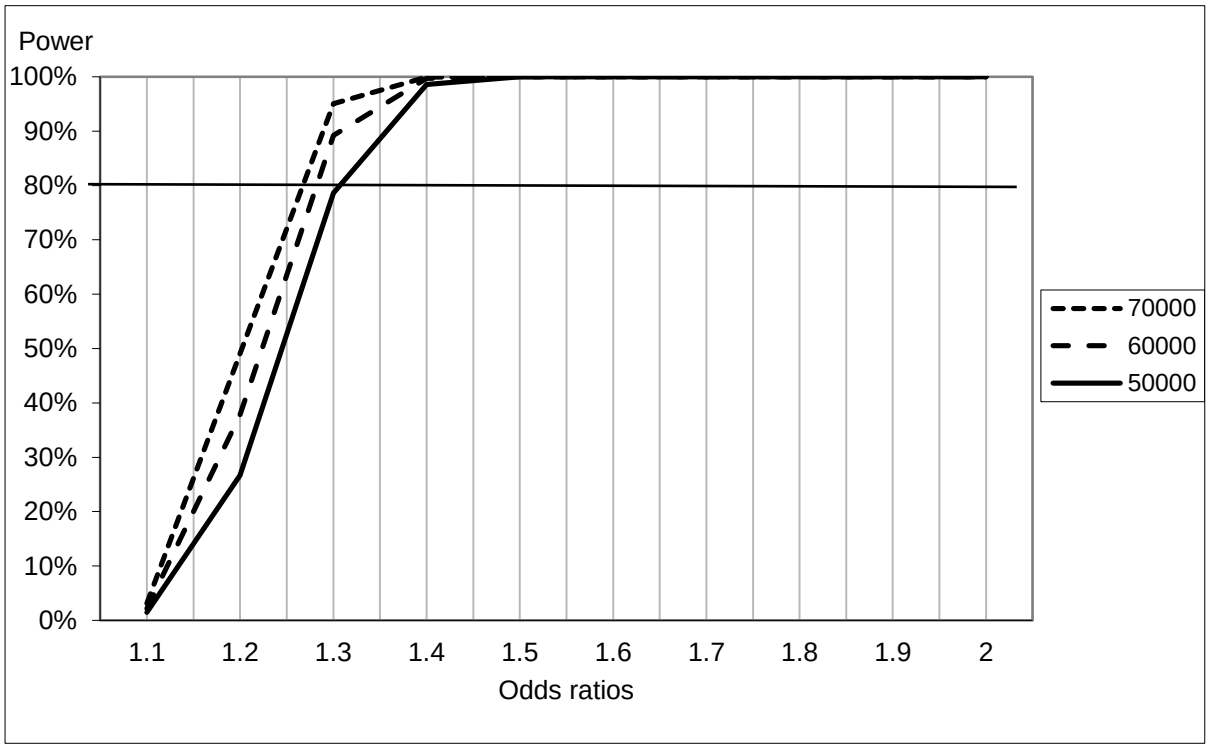


Figure S10: Power curve genetic main effects: outcome 10% MAF 5%

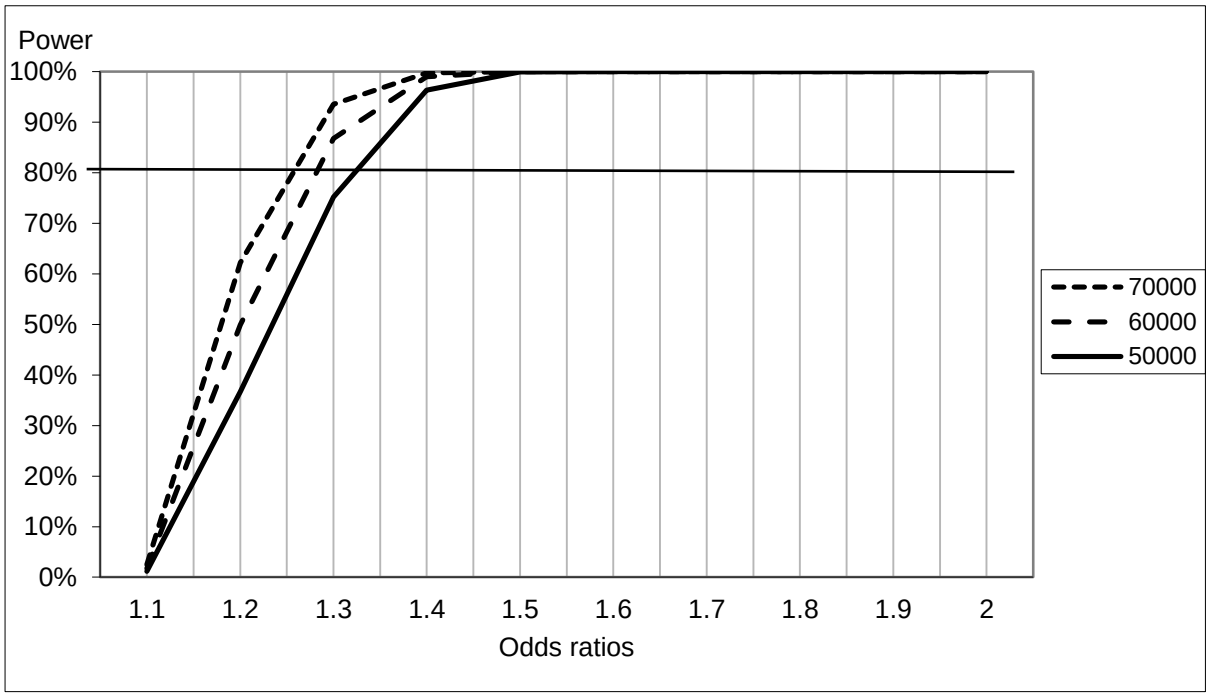



Figure S11: Power curve genetic main effects: outcome 5% MAF 5%

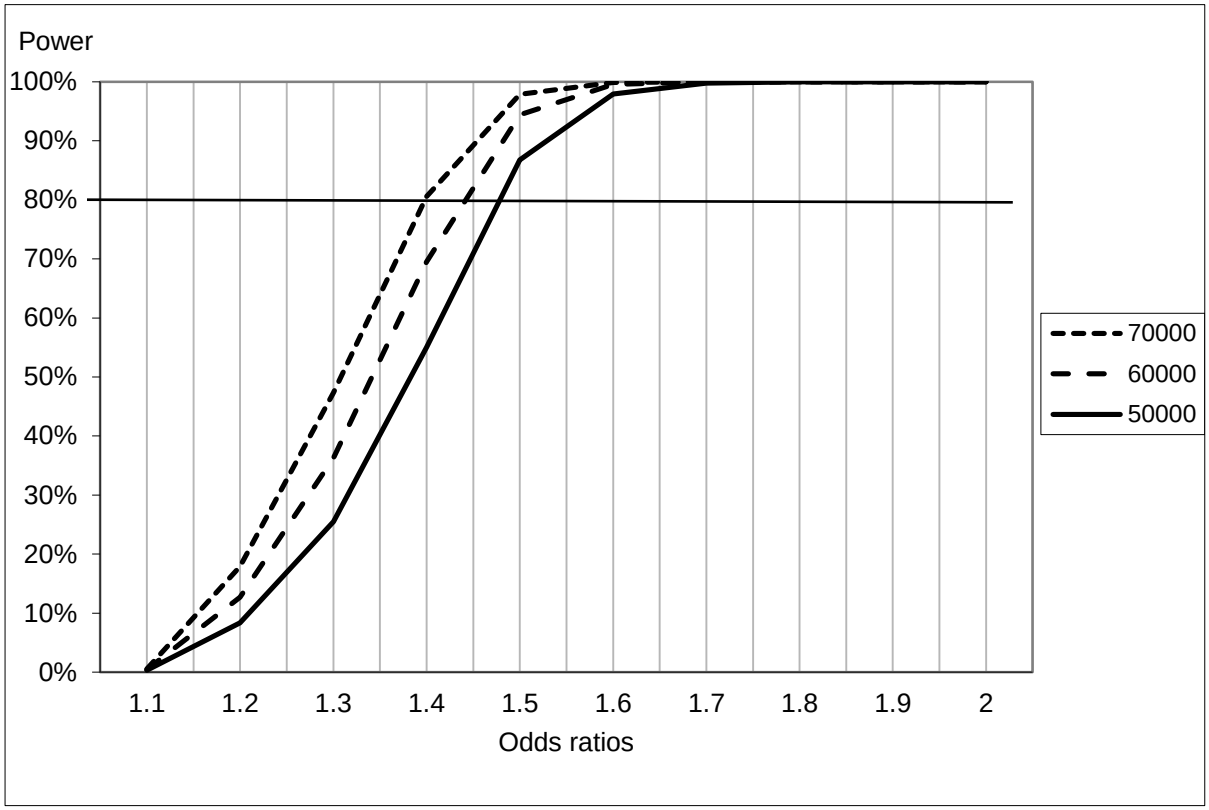
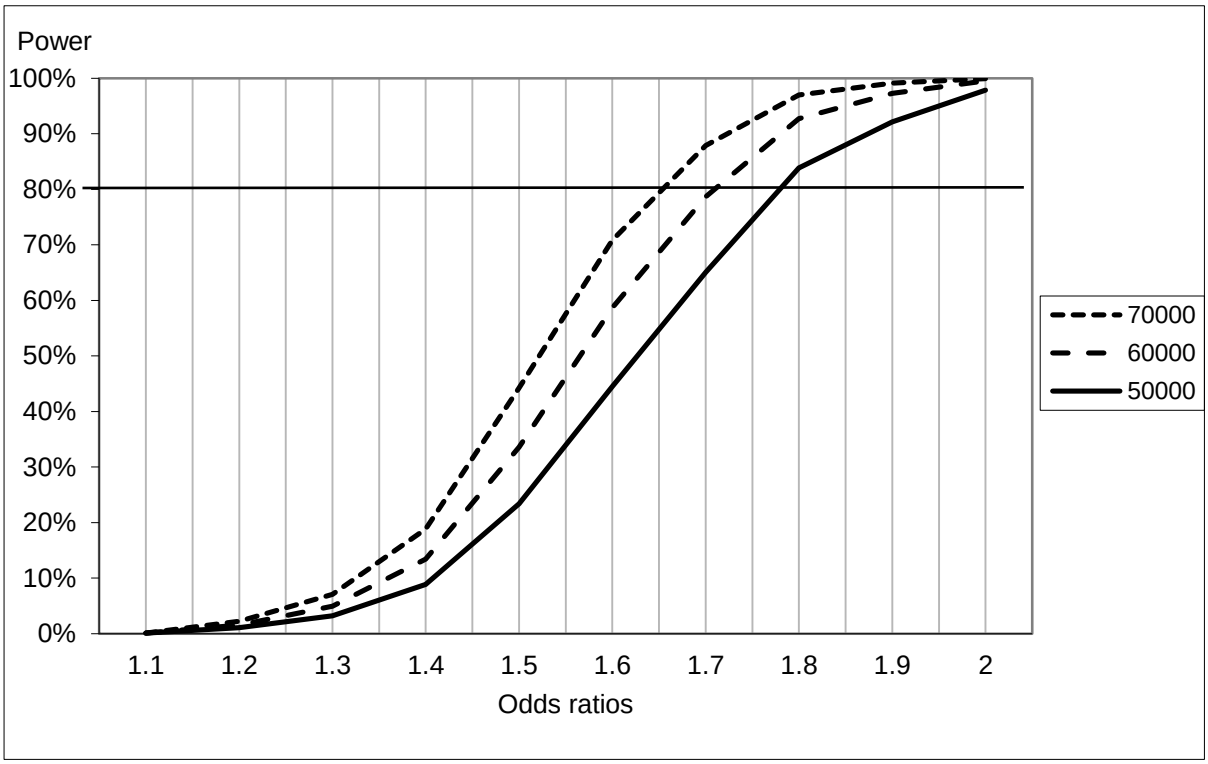


Figure S12: Power curve genetic main effects: outcome 2% MAF 5%




### 6.3.3 Birth Component Design

#### 6.3.3.1 Meeting the scientific objectives of Life Study

Life Study has been designed to achieve a scale (numbers of participants) and a depth (nature and extent of the information to be collected) that will provide data to inform important research areas relating to early childhood development. While this objective could be addressed partially via the data resources to be created via the Pregnancy Component alone, the Birth Component will enable research findings from the Pregnancy Component to be generalized to the UK population of births. The Birth Component is designed to complement, extend and add value to data collected from the geographically focused Pregnancy Component.

Life Study will provide an integrated large scale data resource with information on both biomedical and social factors enabling the use of rich data – collected in the Pregnancy Component – to accurately capture the exposures and potential confounders prior to birth, and in the Birth Component to explore the population impact of these exposures on the outcomes of interest. The Birth Component offers the opportunity to analyse the interplay of factors that cannot be reliably tested in the Pregnancy Component (urban/rural effects

for example) and by relating this to the Pregnancy Component to understand any selection biases or confounding structures within and across each sample.

#### 6.3.3.2 Sample design for the Birth Component

Sampling for the Birth Component has two stages. The first stage consists of the selecting a random sample of Primary Sampling Units (PSUs). The second stage is the selection of a sample of births from within each PSU. Middle Super Output Areas (MSOAs) are likely to be appropriate as PSUs as 2011 Census of Population data is available at this level of geographical detail, providing indicators of ethnicity and social background, and there is a reasonably balanced population distribution across MSOAs.

The Birth Component sample will be based on birth registration records as these include information on the age, address, name and occupation and country of birth of the mother (and the father for married couples and those who are not married but co-register the birth). In England and Wales, birth records include linked information provided by the midwife when registering the baby to obtain the NHS number (including birth weight, gestation and ethnicity of the mother). The allocation of birth records to PSUs will involve the statistical authorities for England and Wales, Scotland and Northern Ireland.

After sampling procedures have been agreed with the national statistical agencies (or the Data Linkage Service) they will be tested in a 'dry run' before the sampling procedure goes live to ensure that the processes are understood and work as intended within the desired timeframe.

### 6.3.4 Harmonisation of the Pregnancy and Birth Components

#### 6.3.4.1 Data analysis: the user

A set of statistical weights are required to allow the research user to analyse the Life Study data as a single integrated dataset, rather than as separate Pregnancy Component and Birth Component samples. This facilitates inferences to the whole population of UK births.

The weights that are produced should be straightforward to apply in analyses with appropriate guidance to users. Most software packages will provide a facility for weighted models and associated robust standard errors. For the clustering aspect of the sample (over both components) it is suggested that multilevel models are used to take account of cluster variation. Pilot analyses will be carried out before data are released to study any issues that may arise and provide guidance for users. Information about the computation of weights will also be available to all users. The use of multiple imputation will be studied.

#### 6.3.4.2 Temporal alignment of sampling

Reliably generalising from the Pregnancy Component to the national population using information from the Birth Component requires that the two samples are recruited in concert. The potential for evaluating secular trends makes it essential that information from the Pregnancy Component can be anchored in information derived from a Birth Component that is contemporaneous.

Birth Component interviews will be timed therefore to correspond with the 6 month interviews in the Pregnancy Component. Over the four years of the study, this implies that the Birth Component 6 month interviews should be completed at the rate of approximately 420 per month. To gain temporal alignment with the first 6 month interviews conducted at Life Study Centres, home visits with the mother and fathers/partners within the Birth Component will commence in March 2015.

#### 6.3.4.3 Weighting and overlap between the two samples

The methods to be used for the calculation of sample weights for the Birth Group depend on the extent to which access can be given to the personal information contained within birth records (including the linked maternity records) for all live births in each sample period. Access to national birth registrations is being sought from ONS under Approved Researcher Status as set out in the Statistics and Registration Act 2007 and would permit Life Study statisticians to access data through the ONS virtual micro-laboratory and to analyse these records having added a response marker to the national data files. This procedure would be performed for both Birth Component and Pregnancy Component samples to provide users with the means to integrate the two samples for analytical purposes, thereby achieving an increase in the power of statistical estimates derived for the Life Study.

## 6.4 Appendix 4: Pregnancy Component – selecting maternity units

### 6.4.1 Background

In the original submission (mid 2009) data for the year 2007 were extracted from the national births register for England and Wales and from the Health Care Commission Survey and used for the sampling frame to categorise births by residence and by maternal ethnicity. This information was then used to review and identify potential geographic locations for Life Study Centres, taking account of the co-located maternity units and their birth rates and the ethnicity of the births delivering in those units.

### 6.4.2 Principles for maternity unit selection

An important scientific objective was to over-represent the main black and minority ethnic [BME] groups. BME births are clustered in the UK, as most BME groups reside in England; 98% of the Asian and 98% of the Black population live in urban areas. As a consequence of this, there will be some under-representation of those living in rural areas and the most socially deprived quintiles may be overrepresented. These implications were discussed at peer review and subsequently, and these trade-offs were agreed to be acceptable.

Each Life Study Centre should be located in proximity to the maternity units 'feeding' into it, to support good recruitment rates over the time period. In the original application it was assumed that women would not travel more than 30 km to attend a Life Study Centre.

### 6.4.3 Original modeling (2009)

Modelling of births to identify choice of maternity units for the original application was carried out at the Small Area Health Statistics Unit (SAHSU), Imperial College, using confidential datasets including full postcode of residence registered at birth, under special licence. Additional information was provided by the National Perinatal Epidemiology Unit (NPEU). Preliminary modelling assumed a 35% recruitment rate, selected as an extremely conservative and achievable figure, although the recruitment rate is likely to be considerably higher based on experience from ALSPAC and the Millennium Cohort Study (around 70%) and the Born in Bradford cohort study (80%).

In the original application ten Life Study Centres were proposed but this was reduced to eight Life Study Centres (in England, Wales and Scotland) in order to create the resources needed to meet the requirement to include a national probability sample (to receive home visits as in the Millennium Cohort Study). A Life Study Centre in Northern Ireland was not considered cost effective given the population density. It was estimated that these eight centres would result in a recruited sample of 93,000 women and babies.

### 6.4.4 Updating the maternity unit model in the preparatory phase (2012)

Work to update the maternity unit figures and create a revised list of eligible maternity units for the study was undertaken at the SAHSU, with additional advice from the NPEU and working closely with the Life Study team. All births in 2010 recorded in the national births register, maintained by the Office for National Statistics (ONS) and held at the SAHSU, were mapped by postcode of residence at the time of birth and by maternity unit at delivery in order to map the catchment areas of the various maternity units. Based on these data, the number of maternity units and the numbers of births in each maternity unit that would fall into different distance bands from the proposed Life Study Centres (5 and 10km) were calculated.

The choice of maternity units was driven by a rich mix of maternal ethnicity (based on the Care Quality Commission's Maternity services survey 2010), the unit's clinical network and the compactness of the catchment area. The location of Life Study Centres were selected based on the proximity to the maternity units, public transport hubs and shopping areas.

Estimates were made for different recruitment response rates, namely 50%, 60% and 70% response rates respectively and for 12, 18 and 24 month durations of recruitment. The modelling assumed that response rates are similar across the different ethnic groups. The ONS prediction for a 5% increase in births from 2010 to 2014/2015 when recruitment to the main study will start was also taken into account (% increase 2010 to 2014: 4.9%; % increase 2010 to 2015: 4.8%).

These data suggested that a target sample of over 93,000 births might be achieved with an 18 months recruitment period depending on response rates.

### 6.4.5 Revisions to the maternity unit model in the pilot phase (2013)

The original Life Study design was based on an 8 centre model. During the pilot phase, it became clear that maintaining 8 centres would not be feasible within the original budget. In order to maintain the scientific value of the original proposal, a revised design required:

- a sufficiently large sample size to address the original scientific objectives,
- a good ethnic, socioeconomic and geographical diversity among participants recruited,
- at least one prenatal visit to ensure a rich resource of pregnancy data, and
- two postnatal visits to maintain the richness of phenotypic data.

During 2013, business-processing and cost models were scrutinised by the Life Study SSC and LSSAC, as well as representatives of the funding bodies. The preferred revised option for Life Study was to recruit from four Centres for 30 months with two postnatal visits. This maintained a large sample size of over 60,000 babies with a 50% recruitment rate, and ensured good ethnic, socioeconomic and geographical mix and maintained two visits.

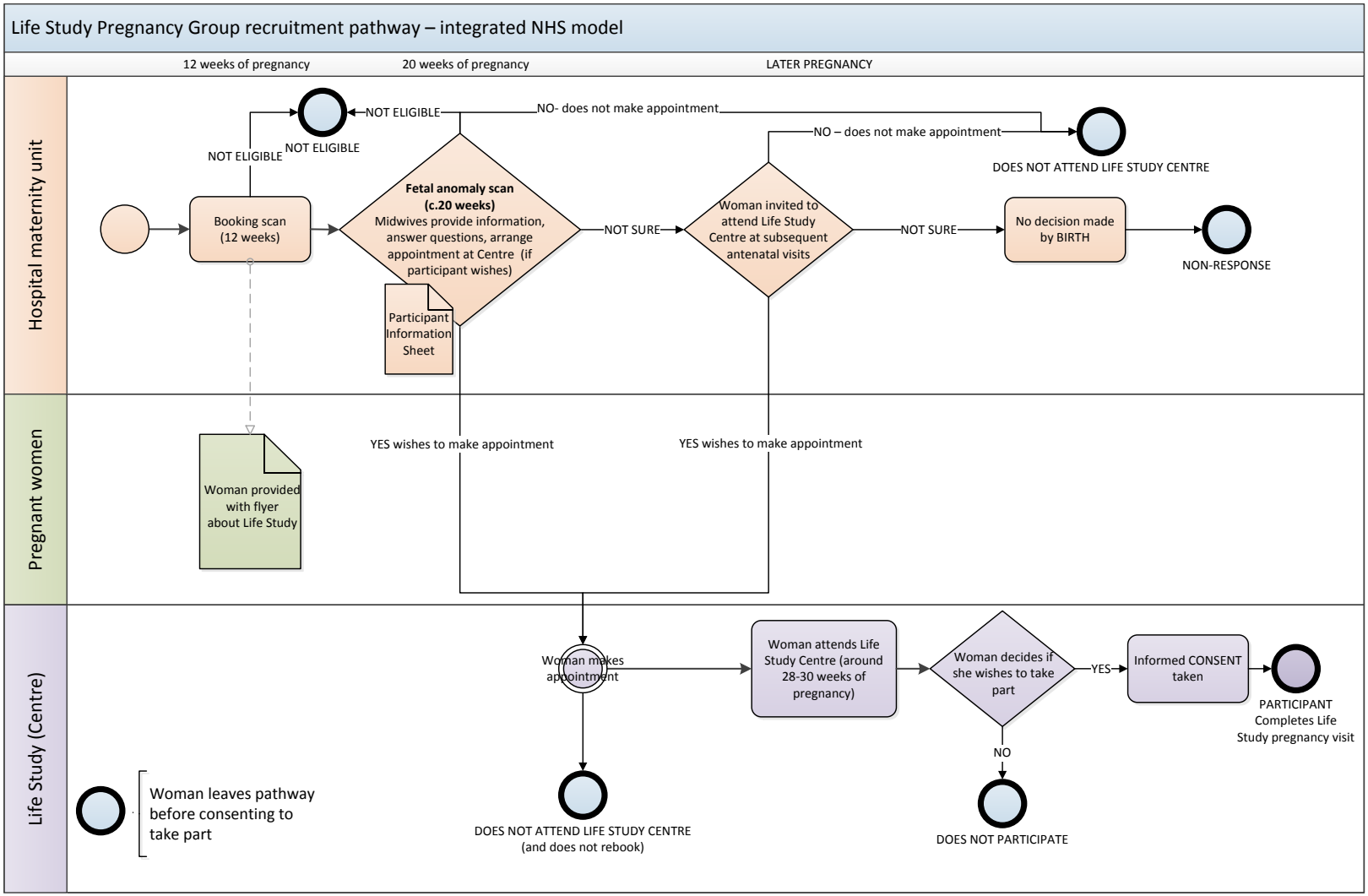
### 6.4.6 Implications of evaluation at end of Phase 1

As significant uncertainties persist in relation to recruitment rate and operational complexity, it was agreed that the first two centres would open and be evaluated in Phase 1. The opening of further centres in Phase 2 (mid-2016) will depend upon successful recruitment and operations in Phase 1. This evaluation will take place around the time of Government Gateway Review 4b.

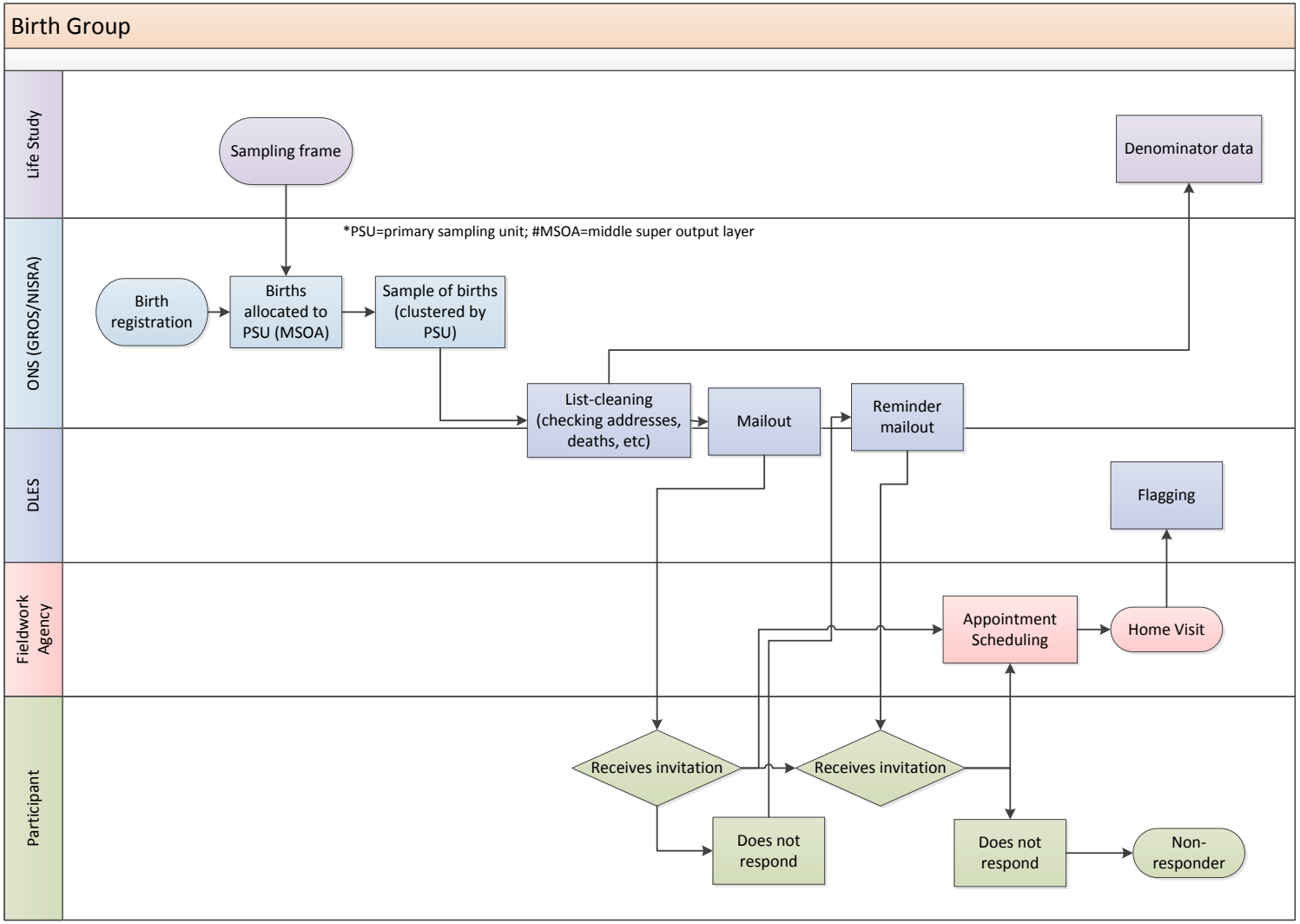
If the study is unable to progress to Phase 2, Life Study Centres 1 and 2 will complete data collection and postnatal visits on all participants recruited and maintain longitudinal follow-up until October 2017. To ensure that data from the UK-wide representative Birth Component sample can be integrated with the Phase 1 Pregnancy Component sample, the Birth Component will commence recruiting in Phase 1 and will continue to recruit alongside the Pregnancy Component until it reaches the target sample size of 20,000 participants.

The number of recruited participants in Phase 1 is still likely to be greater than total sample sizes in previous cohorts. Phase 1 alone would provide a valuable nationally representative resource with greater pregnancy coverage and richness of biomedical data than previously achieved in a national longitudinal cohort study, despite potential limitations in addressing some of the original research objectives. The full potential of Life Study to address the original study aims will be achieved by Phases 1 and 2 combined.

## 6.5 Appendix 5: Recruitment Pathways




Note: Pregnancy Component referred to as Pregnancy Group in this diagram




Note: Birth Component referred to as Birth Group in this diagram

## 6.6 Appendix 6: Protocols for the physical measurements

The Standard Operating Procedures for anthropometry, vision and child development assessments are available as separate reports for download on the 'Resources' page of the Life Study website www.lifestudy.ac.uk.

## 6.7 Appendix 7: Survey and Interview Schedules

Appendix 7 provides an overview of the survey and interview questions included in the final scientific protocol. All questionnaires which were designed, scripted and, where relevant, were in use at the time Life Study closed, are available as separate reports for download on the 'Resources' page of the Life Study website www.lifestudy.ac.uk.

### 6.7.1 Background to survey and interview topics

#### 6.7.1.1 Parents and families

The topics and question areas included within the 'Parents and Families' module are shown in Figure 1.

Figure 1: Parents and families module


##### 6.7.1.1.1 Identity: ethnic, national and other identities

The large study sample will allow analyses within and between different cultural and ethnic groups, including the relationship between identity and child outcomes, and intergenerational social mobility among families from different cultural backgrounds.

Life Study will collect information on the:

- cultural, ethnic and religious identities of the child's mother and partner;
- migration status of parents and grandparents
- languages used in the home and with the baby.

#### 6.7.1.1.2 Parents' health and lifestyle

A significant focus will be on parents' health lifestyle during and after pregnancy, including physical activity, alcohol, smoking, diet and nutrition, and their influence on child outcomes. Pregnancy and the early postnatal period are also times when women and their partners make behavioural changes, including quitting or reducing smoking and alcohol intake, changing their diet and often reducing or changing the type of physical activity they commonly undertake. Obesity or greater weight gain in pregnancy are associated with more extreme vascular and metabolic changes and increased risk of later adverse outcomes in women. Little is known about the levels and impact of maternal physical activity in pregnancy on infant and longer-term child outcomes.

Life Study will collect information about:

- parents' views of their own health, including longstanding limiting illness
- hospital admissions
- regular medications.

#### 6.7.1.1.3 Mental health, well-being and cognitive and non-cognitive traits

Life Study will enquire about parental mental health, parental well-being, parents' cognition (IQ), and non-cognitive constructs, such as parental self-efficacy and personality traits. A wider range of mental health disorders will be explored in both mothers and partners than have typically been covered in national birth cohort studies, including anxiety and depression, past mental health problems, ADHD and autism traits. This will allow an understanding of how both mothers' and fathers' mental health contributes to a range of emotional and behavioural disorders that present in young children, many of which have been increasing in prevalence in recent years. Repeated observations will help clarify the effects on children of enduring compared to episodic problems.

Measures of IQ and personality traits will be collected from both mothers and partners. These will be key for understanding the strong intergenerational links in cognitive ability and in non-cognitive traits between parents and their children, and help map the complex interplay between parenting behaviours, environmental and genetic factors.

#### 6.7.1.1.4 Education and employment, and financial situation

Birth outcomes and early infant development are strongly patterned by parental occupation, education, and measures of family economic status such as income and wealth. Life Study will provide important new insights into the early causes and mechanisms for the transmission of disadvantage across generations. It will allow researchers to understand the impact on developmental outcomes of the interactions between social and socio-economic inequalities, biological and environmental factors, and parental behaviours before birth and in the first year after birth.

Questions on education, employment and occupation have been designed to ensure continuity and comparability with the key socio-economic indicators of previous birth cohort studies. This will enable cross-cohort comparisons on important policy issues such as social mobility. Importantly, pregnancy is also a time of social and economic change for a woman, her partner and her children. These changes are likely to be inter-related and have lasting effects on the future health, social and economic activity and wellbeing of the mother, partner and child. The birth of a child is also associated with changes to working patterns for both parents. Life Study will collect detailed information, pre- and post-birth, to allow analyses of how these critical labour supply decisions affect the future health and wellbeing of children. This will also include information on grandparents' occupation and employment.

Understanding how poverty and early child outcomes are linked will be vital. Measures of income and wealth, and parents' subjective assessments of financial well-being will provide important information about the short- and longer-term financial resources available to the child. Information to be collected on parents' educational qualifications and books in the home will provide an important measure of the cultural capital available to young children, which is an important contributor to children's outcomes such as their readiness for school.

#### 6.7.1.1.5 Family structure and relationships

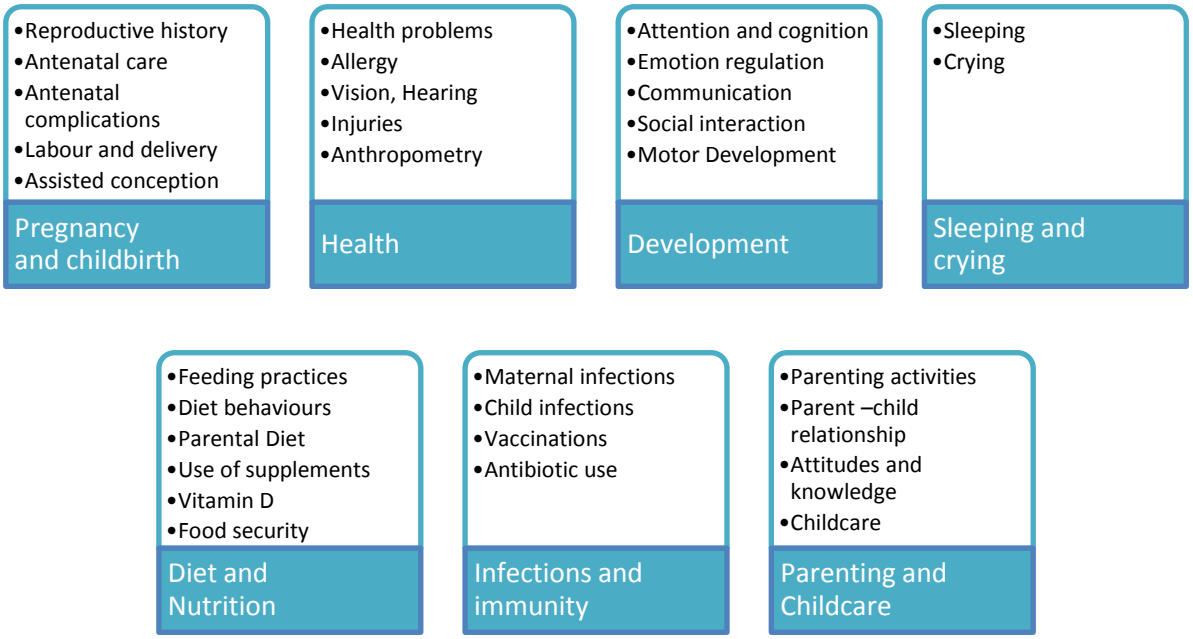
The study will capture a comprehensive picture of the structure of the family into which the new child is born, and the stability of family composition in the first year of life. Parental relationship quality and stability are known to be extremely important determinants of children's social and emotional development, and the birth of a new child typically puts pressures on intimate partnerships. This study will collect information on partnership dissolution and formation, and measures of relationship quality from mothers and partners during pregnancy. Maternal assessments of relationship quality will be collected at repeated time points, so the effects of changes from pre- to post-birth can be assessed in relation to the development of the child.

The study will also collect repeated measures from the mother of the engagement of resident fathers and partners in household duties and child-rearing activities, and the degree of contact between the child and non-resident fathers. It is also anticipated that same-sex parents will be recruited to the study in significant numbers, allowing the first detailed analyses of parenting and child outcomes among this group. An enhancement to Life Study is also being developed, which will increase engagement with partners and fathers, and facilitate direct contact with this group after the birth of the child.

#### 6.7.1.2 Infants

Figure 2 sets out the topics within the 'Infant' module. These cover a wide range of information to be collected about the infant itself, his or her interactions with parents, childcare and the wider family, as well as pregnancy and childbirth.

Figure 2: Infants - topics and question modules




##### 6.7.1.2.1 Pregnancy and birth

Pregnancy is a metabolic challenge in which major changes to glucose and insulin metabolism and to vascular flow and function take place in order to ensure adequate nutrition for normal growth and development of the fetus. Extreme vascular and metabolic changes can result in diagnoses of pregnancy-induced high blood pressure or diabetes, which are associated with future adverse cardiovascular and metabolic disorders in the mother. It is unclear whether there are more subtle changes that are also associated with future adverse health outcomes in the child as well as the mother. Life Study will allow us to examine the association of weight, blood pressure, glucose, insulin and lipids in pregnancy with outcomes in the mother and child at 12 months after birth, as well as the extent to which any of these associations are related to socioeconomic or lifestyle factors, pre-existing diagnoses, or if associations differ with maternal age, ethnicity or parity. Information will be collected about past maternal reproductive history, the current pregnancy (including pregnancy-induced complications) and information about the labour and delivery. Weight and body fat will be measured during and at 12 months after pregnancy (see anthropometry), and blood samples collected to allow measurement of glucose (glycated haemoglobin), as well as to allow additional analyses to investigate the

influence of maternal and fetal genotype and examine the influence of vitamin D sufficiency, iodine sufficiency and thyroid function during pregnancy on mother and child outcomes at 12 months after birth.

Around 1-2% of all babies born in the UK are the result of IVF and other assisted reproductive technologies (ART), thus the short and longer term health outcomes for children of these conceptions and their mothers is of key interest. ART is associated with increased numbers of multiple births which result in adverse pregnancy outcomes, mediated in part through prematurity. It is often difficult to determine whether adverse consequences are due to ART or related to multiple births, prematurity and the underlying reasons for the mother's infertility. There have been virtually no useful large scale epidemiological research addressing the outcomes of ART in the UK, and Life Study represents an important opportunity to collect data on assisted conception and mother and child outcomes in a large longitudinal cohort. Changes in the legal framework governing the HFEA register offer an opportunity for record linkage.

#### 6.7.1.2.2 Child health

Children's health has long term impacts not only on their health and well-being in later life, but also impacts on other aspects of later life such as educational outcomes, employment, and income. Life Study affords both an opportunity to explore factors associated with poor health and also look longitudinally at outcomes associated with poor health during childhood. Life Study will gather information on the health of the infants starting from the immediate period after birth. Those who were born preterm, with congenital disorders, or required special or neonatal intensive care will be identified so that more detailed information on both the health problems and treatments required can be sought through record linkage. Life Study will include mothers' views on the general health of the infants and whether they develop any longstanding illnesses. The study will also collect information on any health problems, which have either resulted in contact with a health professional or admission to a hospital, and medications taken regularly. More detailed information on children's health will be obtained through record linkage to a number of 'health' related databases.

Asthma is an important cause of reduced quality of life, use of health care services, long-term use of medication and mortality across the whole spectrum of age, sex, ethnicity, socioeconomic status and geographical location. The prevalence of asthma increased over the last four decades of the 20th century with a stabilising over more recent years. Whilst numerous theories have been put forward none adequately explain these trends. At an individual level, the most powerful risk factor for asthma is a history of atopic disease such as atopic eczema or allergic rhinitis. Life study will collect information on these conditions both in the infants and their families along with information on infections and immunity,

environmental pollutants and other factors of potential relevance. Such rich information may assist in developing our understanding of this important condition.

In addition to physical measurements of vision in the infants and parents, mothers will be asked questions concerning the child's vision and any problems. Mother's and partners will also be asked about vision problems in their family and the treatments required. Similar questions will be asked in relation to hearing problems.

Immunisation is one of the key public health interventions for saving lives. Life study will gather an immunisation history plus mother's reasons for their child not being up-to-date or rejecting vaccines. No other cohort has been able to look at the timeliness of immunisations so this will provide a unique opportunity. Immunisation status and determinants of vaccine uptake are important to inform policy as well as being a marker of other health related behaviour and in particular of health beliefs.

Injury remains one of the main causes of death and morbidity in childhood in the western world and accounts for significant health service utilisation. Infants younger than one year are particularly vulnerable because they are completely dependent on their caregivers for all their basic needs. Unintentional injuries are socially distributed and this socioeconomic gradient is far more marked amongst younger children. Most injuries to infants occur within the home environment. Life study will collect information on the frequency of injuries leading to medical attention and the nature of the injuries. This in conjunction with information about family circumstances and the home environment will help to inform policies for injury prevention.

#### 6.7.1.2.3 Child development

Neuropsychiatric and developmental disorders in children are relatively common, often enduring and have high costs to individuals, families and society. Affected children are at higher risk of educational difficulties, with consequent implications for economic and social success in later life. Such disorders begin in infancy and early childhood and new tools are increasingly becoming available to diagnose these at an early age. Trends in cohort data over time reveal an increase in disruptive behaviour and emotional problems, including in autism spectrum disorders and attention deficit hyperactivity disorder (ADHD). Whilst neurodevelopmental and neuropsychiatric disorders have been a focus of earlier cohorts, no previous national cohort has covered the range of developmental disorders proposed for investigation in this study, nor have they undertaken prospective measurement of prenatal and early life precursors to childhood disorders. This study will include both paternal and maternal risk factors and use direct observational measures to supplement validated questionnaires.

Key areas of interest are:

- **Attention and cognition:** Early attention and processing of visual stimuli has been shown to predict later cognitive ability or learning difficulties and to have implications for development of ADHD.
- **Emotion regulation:** Infants' early ability to regulate emotion in response to novelty and frustration appears to predict later emotional and behavioural disorders.
- **Communication and language:** Infants' early joint attention skills plus parental language appears to predict later language and communication abilities
- **Social interaction:** Early parent-infant interaction, which promotes later emotional development and the ability to form close relationships.

The six month visit will be adjusted for the child's gestational age at birth by timing it from the estimated date of delivery at the 28 week pregnancy visit. This will ensure that babies who are born prematurely (before 37 completed weeks of pregnancy) will be invited to attend for developmental tests and observations at an appropriate stage of their development, and will be sufficiently mature to take part in the assessment activities.

#### 6.7.1.2.4 Sleeping and crying

Around one-quarter of infants do not have a consolidated sleep pattern ('sleep through the night') by one year of age. Night waking and related infant sleep problems have been associated with difficult temperaments and behaviour problems in younger children, poorer neurobehavioural functioning in older children and to parental stress. In Life Study, validated screening instruments will be used to characterise infant sleep patterns and identify sleep problems. This will support further investigation of the relationship with other measures of infant temperament, parent health and long-term outcomes. Infant crying behaviour has been associated with infant attributes, such as temperament, feeding and sleep patterns, as well as with extrinsic factors such as parent depression or anxiety. Life Study provides an opportunity to observe, in a longitudinal study of a normative population, the association of crying, sleeping and feeding routines in early life with factors such as parent and child interaction, the socio-economic and cultural environment and the infant's intrinsic temperament.

#### 6.7.1.2.5 Diet and Nutrition

Diet and obesity are important risk factors for a range of serious non-communicable diseases, including cancer, cardiovascular disease, and diabetes. Food choices are shaped by a complex interplay of individual, family and environmental factors. Life Study provides an opportunity to understand how key maternal factors, such as maternal diet, nutrition, eating habits and weight-related behaviours, may influence early childhood experiences related to diet and feeding, as well as the long-term health outcomes for children. There is the additional opportunity to look at how these experiences, and the influences on them,

differ across ethnic, cultural and socio-economic groups. Specific attention will be given to feeding, including feeding intentions in pregnancy, the impact of wider social and family networks (such as grandparents) on feeding practices, duration of breastfeeding and weaning practices.

The nutritional content of the diet will be investigated, particularly with regard to iodine sufficiency, Vitamin D sufficiency and the use of dietary supplements, and the implications of these for infant growth and development.

Recent research from Southampton has also highlighted that up to 5% of households with young children may experience 'food insecurity', or limited/uncertain access to sufficient nutritious food. Children living in food insecure households have a poorer quality diet, with implications for long-term health and neurological development. Life Study will collect data to define food security across the UK population and to look at the long-term outcomes for children.

#### 6.7.1.2.6 Infections and immunity

Microorganisms are an important environmental exposure that influences morbidity and mortality throughout childhood and later life. Life Study will address key questions about the role of infection and immunity as determinants of health, disease, well-being and development. The human immune response is influenced by infection and according to the timing of infection, the organism, host and microbe genetics and inherited or acquired immunity. Likelihood of infection and individual immune responses are affected by geography, culture and genetic profile. The timing of microbial colonisation of the newborn (particularly the gut microbiome) may have important implications for future health and disease. Only in recent years have the methods become available to investigate at scale the interaction between and the relative contribution of social, environmental, microbial and host factors in this complex process. Life Study offers a unique opportunity to explore the interplay of these processes from early life onwards.

In addition to questions about infections, vaccinations and antibiotic use, specific biological samples will be collected at the Life Study Centre visit, at birth or retrieved from leftover stored samples (e.g. newborn bloodspot screening programme or maternity booking bloods).

#### 6.7.1.2.7 Parenting and childcare

The sensitivity and responsiveness of parents and care-givers to their babies, and the quality of stimulation provided in the home and other settings, are known to be critical for young children's development. In Life Study we will combine the piloting of innovative direct observational measures of mother-child interactions, with questionnaire instruments. The

questions are designed to capture maternal attachment (to the developing fetus during pregnancy, and then to the baby), maternal beliefs, attitudes and knowledge about infant development, and the frequency of activities such as singing and reading to the baby, and play materials in the home.

For the mothers who return to work within the baby's first year (around half of all mothers), the duration and quality of childcare arrangements are also important for the child's development and well-being. This study will collect information about who looks after the baby, for how many hours each week, when this started, and the cost of childcare. Suitable measures of childcare quality will be used.

#### 6.7.1.3 Neighbourhoods and Environment

Ecological theories suggest that a child's development should be viewed as an evolving interaction between the person and the environment, and predicts multiple interacting influences on the child at the level of the family, the neighbourhood and the wider community. Figure 3 sets out the topics and question modules, grouped under Neighbourhoods and Environment.

Figure 3: Neighbourhoods and Environment: topics and question modules


##### 6.7.1.3.1 Social networks

Social support systems may either play a protective role, mitigating the effects of stress and other risk factors or create additional stressors through non-supportive, conflictual or interfering interactions. An innovation of this study, compared to other national and sub-national birth cohort studies will be to collect information on both positive and negative

qualities of friendships and relationships with relatives, as well as capturing the way in which new technologies (such as social media networks) facilitate social interactions among mothers with young babies. Measures will be taken both for mothers and their partners.

#### 6.7.1.3.2 Neighbourhoods and housing conditions

The study will collect information on potentially positive aspects of local areas in relation to parents and children, such as community-belonging, participation and trust, access to local area services and to green and open spaces. Many of these relate strongly to the social capital available to the family and child. Information on neighbourhoods can also be enhanced with detailed post-code level measures of deprivation, local labour market conditions and environmental factors.

The study will also collect information on housing conditions, including measures that are likely to directly impact on child development, health and well-being, such as over-crowding and damp.

#### 6.7.1.3.3 Environmental pollutants

Chronic exposure to potentially toxic substances in the environment is a fact of modern life. The environment and its possible effects on health have become major issues affecting public health and public perception of risk. During the prenatal period the baby is more sensitive and potentially vulnerable to harm from even small quantities of environmental toxicants, which can have lifelong impacts on health. In Life Study, the initial contact with participants during the mother's pregnancy provides a unique opportunity to monitor environmental exposures in utero, and through the first year after birth. Questions relating to the environment and health will cover five exposure themes: air pollution, drinking water disinfection by-products, radio frequency and electromagnetic frequency exposure, persistent organic pollutants (particularly chemical exposures in the home), and noise.

These will allow examination of hypotheses relating to the relationship between:

- exposure to indoor and outdoor air pollutants (particularly arising from traffic) and risk of a) adverse birth outcomes and b) allergic and respiratory disorders
- exposure to chlorination by-products in public water supplies and risk of adverse birth outcomes
- radiofrequency (RF) exposure and a) adverse birth outcomes (low birth weight and congenital malformations), and b) cognitive development in early childhood
- prenatal exposure and childhood dietary exposure to persistent organic pollutants (POPs), and longer term neurobehavioural/cognitive function in children, e.g. ADHD
- the effect of noise exposure on longer term neurobehavioural/cognitive function in children.

### 6.7.2 Piloting and revisions to the questionnaire

NatCen, a fieldwork agency, was commissioned to pilot the Life Study questionnaire for the pregnancy component. Results from participant and interviewer evaluation led to changes to the final questionnaire and interview schedules. The pregnancy, 6-month and 12-month visit questionnaires were also longer than desired. The Life Study SSC reviewed and amended the questionnaires in the light of this experience and also the early experience of its use in the first Life Study Centre.

Ipsos MORI, the fieldwork agency appointed to conduct the birth component, piloted the six month mother and resident father/partner questionnaires in 2015.

All final versions are available from the 'Resources' page of the Life Study website.[1]

[1] www.lifestudy.ac.uk