RESEARCHING PRE-TERM BIRTH:

THE ORACLE TRIAL AND CHILDREN STUDY

THESIS SUBMITTED FOR PHD BY PUBLISHED WORK AT UNIVERSITY OF LEICESTER

NOVEMBER 2008

SARA KENYON
ACKNOWLEDGEMENTS

Heartfelt thanks to Mary Dixon-Woods whose idea this submission was and who is a very remarkable woman. Her belief in me and her advice has been pivotal.

Thank you to all the women who joined the ORACLE Trial and to their children for telling us how they were doing. Thank you to the obstetricians and midwives who worked so hard recruiting them.

None of this would have come about without David Taylor, who recognised my ability, and whose influence has changed my life- thank you. Peter Brocklehurst, David Jones, Neil Marlow, Alison Salt and Katie Pike have also been an extraordinary and wonderful group to work with- thank you all. Thank you to Ann Blackburn and Kate Yarrow who have supported me throughout this whole process. Particular thanks to Rebecca Smyth and Amanda Rhodes and all the staff who have worked on both the ORACLE Trial and the Children Study.

Barbara Farrell has also been hugely influential and a great friend- thank you. My thanks also to Carolyn Roth and Ellen Carter who also recognised my abilities before I did. I am lucky enough to enjoy this journey hugely and to have worked with some fantastic people not mentioned here - thank you all. Collaborations with named individuals on each of my papers are listed and much appreciated- there is no doubt their contributions were essential to the achievements of the ORACLE trial and Children Study.

Thank you to my husband Neil, and my children Charlotte and Jack, and Whiskey our dog and apologies for not being at home sometimes when I should have been-I love you all.
CONTENTS

CHAPTER ONE: INTRODUCTION ................................................................. 5
CHAPTER TWO: GENERATING THE EVIDENCE ......................................... 9

THE ORACLE TRIAL

BACKGROUND ............................................................................................... 9
ORGANISATIONAL STRUCTURE OF THE ORACLE TRIAL............................. 10
DESIGN OF ORACLE TRIAL ........................................................................... 10
CHALLENGES ENCOUNTERED ....................................................................... 12
  Recruitment to the ORACLE Trial ........................................................... 12
  Simplification of recruitment procedures ................................................. 12
  Support and training of staff ................................................................... 13
RESULTS OF ORACLE TRIAL ...................................................................... 14
CHANGES IN PRACTICE ................................................................................. 16
  Prescribing for women with PROM ......................................................... 16
  Prescribing for women with SPL ............................................................... 17
  Model of trial recruitment ...................................................................... 17
SUMMARY ................................................................................................... 18

CHAPTER THREE: GENERATING THE EVIDENCE ..................................... 19

THE ORACLE CHILDREN STUDY

BACKGROUND ................................................................................................ 19
ORGANISATIONAL STRUCTURE ................................................................. 20
DESIGN OF THE ORACLE CHILDREN STUDY .............................................. 20
PLANNED ANALYSIS .................................................................................... 22
CHALLENGES ENCOUNTERED ..................................................................... 24
  Design of the questionnaire ................................................................... 24
  Collection of educational attainment data .............................................. 25
THE RESULTS OF THE ORACLE CHILDREN STUDY .................................. 26
  Results for children whose mothers had PROM ....................................... 26
  Results for children whose mothers had SPL .......................................... 26
CHANGES IN PRACTICE ............................................................................... 28
CHAPTER ONE: INTRODUCTION

The rate of preterm birth is 5-9% of all births in Europe, and 12-13% in the United States of America (USA); the rates in both continents are increasing, partly due to the higher number of multiple births associated with assisted conceptions. About 30-35% of preterm births are the result of maternal or fetal disease, but 40-45% of premature births result from spontaneous preterm birth (SPL) and 25-30% from preterm rupture of the membranes (PROM). For families struggling to cope with having a baby in special care, this will be one of the most difficult, emotional and stressful times of their lives, whatever the longer term outcome. The sequelae of preterm birth also pose significant challenges. Children born preterm are at increased risk of major disabilities, such as cerebral palsy, with the risk increasing with decreasing gestation at birth. Many preterm children without disability develop serious behavioural and educational difficulties. The prevention of preterm birth and reduction of associated disability are therefore important health priorities, and are a major focus of my work.

The principle that health care should be “evidence-based” lies at the heart of today’s National Health Service (NHS) but this has not always been the case. Lessons about the importance of evaluation of treatments can readily be demonstrated within maternity and perinatal care. Perhaps the most famous example is that of thalidomide, which became recommended treatment for pregnant women to relieve morning sickness in the late 1950s. By the beginning of the 1960s obstetricians had begun to notice increased numbers of children with severely malformed arms and legs. At the end of 1961 the
manufacturers withdrew thalidomide. Though it took many years before the victims received compensation, it did contribute to the overhaul of the process of drug development and licensing worldwide \(^7\) and underlined the importance of rigorous evaluation of therapies.

Harm does not only result from untested drugs; advice can also be lethal. From the 1950s onwards, Dr Benjamin Spock’s unevaluated advice that babies were best sleeping on their stomachs soon became standard advice for both parents and healthcare professionals.\(^8\) During the 1970s and 1980s there was a steep increase in the numbers of babies dying from Sudden Infant Death Syndrome (SIDS). It was only when the evidence was reviewed systematically\(^9\) that the link was made and advice given that babies should in fact sleep on their backs. A systematic review has conclusively demonstrated that this is the right advice.\(^10\)

It is perhaps unsurprising that much of the early momentum for evidence-based healthcare came from maternity services, and specifically the National Perinatal Epidemiology Unit (NPEU) in Oxford. Iain Chalmers directed the National Perinatal Epidemiology Unit in Oxford, between 1978 and 1992, and coordinated, with Murray Enkin and Marc Keirse, the base for the work which led to Effective Care in Pregnancy and Childbirth (ECPC), which was first published in 1988\(^11\) together with the development the Oxford Database of Perinatal Trials. This work responded to the challenges raised by Archie Cochrane, who had earlier realised the importance of providing access to reliable information on the effects of treatments to both patients and clinicians and that information should be combined in a systematic and reliable way. His
highly influential book *Effectiveness and Efficiency: Random Reflections on Health Services* \(^1\) is recognised as being of seminal importance in the lay media as well as the medical press, and it has been translated into several languages.\(^2\)

The first Cochrane centre (in Oxford, United Kingdom (UK)) was led by Iain Chalmers and the Cochrane Collaboration was started in 1993. The Collaboration is an international organisation that aims to help people make well-informed decisions about healthcare by preparing, maintaining and promoting the accessibility of systematic reviews of the effects of healthcare interventions. The Cochrane Library now contains systematic reviews in many specialities and subject areas and provides a world renowned standard for systematic reviewing (www.cochrane.org).

Clearly, the ongoing challenge to provide a sound evidence-base to inform practice must be met by using the most appropriate and methodologically rigorous approaches to evaluation. For many evaluative questions in healthcare, the randomised controlled trial (RCT) is seen as the ‘gold standard’, the most powerful method available to test hypotheses of cause and effect between variables within medicine.\(^3\) However, it is not without its critics. One branch of feminism, for example, has argued that the kinds of quantitative knowledge generated using this methodology omits participants’ perspectives and experiences and is embedded in masculine values.\(^4\) There is a middle way. While acknowledging the value of evidence obtained from quantitative methodologies I, along with other researchers, have striven to complement
randomised controlled trials (RCT’s) with qualitative approaches, and to value ‘research on women as participants rather than subjects’.\textsuperscript{16}

The work submitted as the basis of this application for the award of PhD, published over a 20 year period, has been driven by my desire to improve care to women during pregnancy and birth, both by generating high quality scientific evidence to inform practice and by exploring women’s views. This overview will describe the scope and content of my work and reflect on its contribution to the advancement of the subject. The publications that are the basis of my submission (listed in Appendix One and cited as Papers I-XVI) are based on a major randomised controlled trial and long-term follow up study (the ORACLE Trial and Children Study) and accompanying qualitative papers to explore participants’ views. A smaller body of work on women’s views on consenting to surgery and on leadership (Papers XIII-XVI) is also included, but is not a primary focus on this overview. Rather, it is included to further demonstrate my commitment to seeking high quality evidence, particularly relating to patients’ perspectives, to inform the provision of healthcare.
CHAPTER TWO: GENERATING THE EVIDENCE

THE ORACLE TRIAL

Background

In the early 1990s evidence was accumulating that subclinical infection played a substantial part in preterm birth. It was thought plausible that bacterial stimulation of prostaglandins either directly\textsuperscript{17} or indirectly\textsuperscript{18} caused uterine contractions. In women with Pre-term Rupture of Membranes (PROM), positive amniotic fluid cultures for bacteria were found to be present in as many as 75% during labour.\textsuperscript{19} The rates of positive amniotic fluid cultures found in women with Spontaneous Pre-term Labour (SPL) with intact membranes were estimated at 40%.\textsuperscript{20} One body of clinical opinion held that antibiotics might treat the infection, and inhibit progression to preterm birth by interrupting the production of prostaglandins.\textsuperscript{17, 18} However, there was uncertainty as to the effects on the neonate and whether prolongation of pregnancy in a potentially hostile environment would be of benefit.

Evidence in the early 1980s from randomised trials of antibiotics for women with SPL alone was not conclusive\textsuperscript{21} and evidence for women with PROM showed evidence of prolongation of pregnancy and reduction in some recognised markers of neonatal morbidity.\textsuperscript{22} These trials were under-powered to look at neonatal outcomes and there was not felt to be sufficient evidence of benefit to recommend the routine prescription of antibiotics to women in these situations.
A large randomised trial was therefore indicated and this was the basis of the ORACLE trial.

Organisational structure of the ORACLE trial

The ORACLE trial (Overview of the Role of Antibiotics in the Curtailment of Labour and Early delivery) was conceived by David Taylor as a Reader in Obstetrics and Gynaecology in Dundee, together with William Tarnow Mordi (a Senior Lecturer in Neonatology). They designed the ORACLE clinical trial and the Medical Research Council (MRC) funded it in 1992. Professor Taylor was shortly after appointed to a Chair in Leicester and I was appointed as the Research Midwife in 1993 after the pilot study in Scotland had been completed. Initially the management structure and funding was cross-site, between Dundee and Leicester, but this proved ineffective. Following review by the MRC in 1995, Professor Taylor and I took the lead based in Leicester and I became a co-investigator on the grant.

Design of ORACLE trial

ORACLE remains the largest perinatal trial in preterm labour to date. It was a double blind placebo controlled trial designed to test the hypothesis that the treatment of women less than 37 weeks pregnant in either SPL or with PROM with broad spectrum antibiotics (erythromycin or co-amoxiclav) prolonged pregnancy and improved neonatal outcomes. The antibiotics chosen to be tested in the trial provided the broadest range of activity against the pathogens implicated in the genital tract. Women were not eligible to join the trial if they showed overt signs of infection and required antibiotic treatment. The primary
outcome was a composite measure on neonatal health (death, abnormal cerebral ultrasound on discharge from hospital and chronic lung disease (defined as oxygenation at 36 weeks post-conceptual age). Secondary outcomes included other markers of maternal and neonatal health.

Women were randomised to one of four treatment possibilities (both antibiotics, co-amoxiclav alone, erythromycin alone or both placebos) and a 2x 2 factorial design was chosen. This allowed simultaneous investigation of the two interventions, thus saving both time and money. It also allowed both the separate effects of each intervention and of both interventions to be considered, as well as whether there is an additive effect or 'interaction'. See Table 1 below. The sample size required was 10,000 women.

<table>
<thead>
<tr>
<th></th>
<th>Any Co-amoxiclav</th>
<th>No Co-amoxiclav</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Erythromycin</td>
<td>Erythromycin and Co-amoxiclav</td>
<td>Erythromycin only</td>
</tr>
<tr>
<td>No Erythromycin</td>
<td>Co-amoxiclav only</td>
<td>Double placebo</td>
</tr>
</tbody>
</table>

Table 1: Factorial design.
Challenges encountered

Recruitment to the ORACLE Trial

The main trial started in July 1994 and between then and May 2000 (when the trial ended), 4826 women with PROM and 6295 women with SPL were randomised. However, the recruitment of these substantial numbers posed considerable challenges that I was required to resolve. Delays and problems with recruitment of both clinicians and participants in randomised controlled trials (RCTs) are well-recognised, and they have a major impact on costs, feasibility and workloads of trials. A systematic review available at that time illustrated the complexity of the issues involved. The review found the barriers to clinical participation included: time constraints, lack of staff, worry about the impact on doctor patient relationships, concern for patients, loss of professional autonomy, difficulty with the consent procedure, lack of rewards and recognition and an insufficiently interesting research question.

Simplification of recruitment procedures

Following the pilot study in Scotland, 137 women had been randomised from six centres, but clinical staff in the units found both the recruitment and data collection too complex. With the support of more experienced trialists (Richard Peto and Barbara Farrell) from the Clinical Trials Unit in Oxford, I led the redesign of the processes and trial materials to be much simpler. One important, though simple, move included putting all the study materials including a pen, information for participants and study drugs in one box, so it was as easy as possible for staff to recruit participants.
Support and training of staff

Despite these improvements, recruitment was slow and by late 1995 it was apparent that the target sample size would be missed unless action was taken. I identified that many staff in the units were lacking in knowledge and confidence about the trial, and that where there was interested, well-informed and motivated midwife (supported by an obstetrician) recruitment was better. Following a small pilot, funding was secured from the MRC to support 80 midwives part time in the larger units where there was potential to recruit more women. The midwives were trained and supported within their units by four Regional midwives and employed three hours a week to recruit a pre-specified and agreed number of women. I became the Trial Co-ordinator in 1997, with responsibility for the day to day organisation, including the midwives, and ultimately recruitment.

The training given to the midwives was hugely important in achieving the recruitment target. I identified that if a member of staff was not familiar with any procedure relating to the trial, it was unlikely she would approach a potential participant. So, the training focused on familiarising clinicians (midwives and doctors) with eligibility, recruitment procedures and questions likely to be asked by both other clinicians and participants. I recognised there was potential for further education via this network of midwives and, as they attended meetings every six months, I arranged additional training on relevant subjects, such as evaluating evidence and change management, thus further enthusing the midwives involved. Recruitment over the next two and a half years until the close in 2000 more than doubled.
The results of the ORACLE trial were published in *The Lancet* in March 2001 (Papers I and II in Appendix One). The trial showed that, for women with PROM, a reduction in the composite primary outcome in singleton pregnancies and other markers of neonatal morbidity was associated with the prescription of erythromycin. While co-amoxiclav was associated with a prolongation of pregnancy, it was also associated with increases in the number of babies with necrotising enterocolitis (and therefore posed risks). For women with SPL no differences were seen in any measure of maternal or neonatal outcome.

The results of the trial highlighted the difference between the two clinical conditions. More women with PROM gave birth prematurely (85%) than those with SPL alone (35%). This finding caused some academics to question the validity of the results, and in particular to note that the diagnosis of SPL remains imperfect; many women who present with regular painful contractions do not go on to give birth.

The trial generated considerable scientific controversy. A commentary in *The Lancet* suggested that, while the trials had been ‘superbly conducted’, the analysis had not explicitly prespecified singletons as a subgroup and therefore the benefits found could be due to chance. Other correspondence in *The Lancet* went on to question whether the analysis had been the most appropriate for a factorial trial. Many of the concerns arose because of the lack of statistical support during the analysis phase of the trial. A particular concern
focused the emphasis placed on what is termed ‘inside the table’ analysis.\textsuperscript{27} When analysing factorial trials the primary analysis should be ‘at the margins’\textsuperscript{27} - so in this instance the groups who received erythromycin (either on its own or together with co-amoxiclav) should be compared to those who did not receive erythromycin. This is the analysis on which the study is powered and therefore less subject to variation. The analysis ‘inside the table’ of the single cells should only be undertaken as sensitivity analysis.

On reflection, there were indeed some grounds for the concerns expressed: there seems little doubt that the analysis presented in the papers over-emphasised the ‘inside the table’ results. For example, within the abstract a statement was made that:

‘Among all 2415 infants born to women allocated erythromycin only or placebo, fewer had the composite primary outcome in the erythromycin group (151 of 1190 [12.7\%] vs 186 of 1225 [15.2\%], p=0.08) than in the placebo group’.

This was based on a comparison of the erythromycin alone group versus the placebo group. However, when comparing the group who received erythromycin (with or without co-amoxiclav) with those who did not receive erythromycin, no difference was observed (318 of 2397 [13.4\%] vs 349 of 2430 [14.4\%, p=0.32). This would suggest that results are not as clear-cut as the abstract in \textit{The Lancet} paper conveys (\textbf{Paper I }).

In conclusion, although there is some evidence that erythromycin delays labour (both from the ‘inside the table’ and the factorial analysis of erythromycin versus
none comparisons) the validity of the improvements in neonatal morbidity is less certain.

Changes in practice

Changing practice remains challenging and complex.\textsuperscript{28} Despite the criticisms of the methods there is little doubt that the ORACLE Trial changed practice: within six months of publication, 50\% of maternity units reported that they had changed their practice and were now prescribing antibiotics to women with PROM (\textbf{Paper III})

\textit{Prescribing for women with PROM}

The Cochrane review of antibiotics for women with PROM was updated in 2002 following the trial publication and advocated prescription of erythromycin to women with PROM.\textsuperscript{29} This was published as a systematic review in 2004 in the Journal of the \textit{American College of Obstetricians and Gynecologists} and became the most viewed article of that issue (\textbf{Paper IV}). In 2006 The RCOG Green Top Guidelines on care of women with PROM also advocated prescription of erythromycin\textsuperscript{30} as did the guidelines issued in the USA in 2007.\textsuperscript{31} More recently a questionnaire survey carried out in the autumn of 2007 showed that 97\% (159/163) of responders prescribe antibiotics for these women, with 97 \%(154/159) using erythromycin. The majority stated there was evidence of benefit 82 \%(93/113).\textsuperscript{32}
Prescribing for women with SPL

For women with SPL (intact membranes) there are still no official guidelines in the UK, although antibiotics are not routinely prescribed. The Cochrane review on SPL was also updated in 2002 following the trial publication and found no evidence to support routine prescription of antibiotics; indeed the results raised concerns over increased neonatal mortality for those who received antibiotics (RR 1.52, 95% CI 0.99 to 2.34). A questionnaire survey of practice undertaken in 2007 found that 78% (128/163) of responders reported they did not treat these women and the majority 71% (72/101) stated that the evidence of benefit was not conclusive. However, 21% (35/163) stated they did treat these women: with erythromycin (16/35), penicillin (15/35), or ampicillin (2/35). Reasons given included: Group B Streptococcus (GBS) prophylaxis (10/29), and evidence of benefit (9/29). In the USA, Guidelines released in 2003 do not recommend antibiotic treatment for these women, although there is continued widespread prescription of antibiotics, particularly for GBS.

Model of trial recruitment

ORACLE was the first trial to acknowledge fully the potential of involving midwives in what was an obstetric question—women in preterm labour are generally cared for by obstetricians. Involving any clinical group in trial recruitment was not without its potential risks; there was a risk that they might obstruct recruitment, or that they might misunderstand the trial in some way and thus offer inappropriate explanations to women. The key to securing the commitment of midwives was provision of appropriate support and training.
Research was seen by many midwives as something they were not familiar with and therefore they were apprehensive; my job was convincing them that there was nothing to be scared of! Involvement with ORACLE Trial on an equal basis with obstetricians was seen as important by those involved, although it was misinterpreted by some midwives who believed the midwives in ORACLE were merely ‘data collectors’.36 In reality midwives are constantly on Labour Wards, as are nurses on the wards, and have the potential to influence recruitment by both prompting recruitment and also explaining to participants in clear language what any particular study involves. Their role is often unrecognised, undervalued and unrewarded.

It is very encouraging that the model I developed to support recruitment (Paper V) is now used by other perinatal trials, including Magpie37 and two trial currently recruiting: BOOST (Benefits of Oxygen Saturation),38 INFANT (a multicentre randomised controlled trial of an intelligent system to support decision making in the management of labour using the cardiotocogram).39

Summary

Obtaining the evidence to evaluate the prescription of antibiotics (erythromycin and co-amoxiclav) to women without overt infection with either preterm ruptured membranes or spontaneous preterm labour (intact membranes) proved both hugely challenging and rewarding. The process of involving midwives as equal partners continues to influence the maternity research landscape. The results changed practice and continue to do so, although whether the strength of the evidence fully supports the extent of the change in practice is debatable.
CHAPTER THREE: GENERATING THE EVIDENCE

THE ORACLE CHILDREN STUDY

Background

Before the start of the ORACLE Children Study in 2002 there was increasing evidence that, in addition to preterm birth, perinatal infection is an independent antecedent of other disability, particularly cerebral palsy and chronic lung disease. One theory was that perinatal prescription of antibiotics could prevent neurological and respiratory disability by two mechanisms, either by prolonging pregnancy, and/or by eliminating infection. In contrast, it was also thought possible that prolongation of pregnancy might increase rather than decrease disability by continuing fetal exposure to inflammatory cytokines, which have already been implicated in the genesis of neurological damage and chronic lung disease.

The ORACLE Children Study (OCS) was designed as a follow-up to the ORACLE trial to determine whether antibiotics prescribed to women at risk of pre-term labour might reduce the long term sequelaes of preterm birth. The OCS aimed to determine if there were any functional or educational differences in the 8942 children born in the UK to mothers who were randomised to the original ORACLE trial. Data were collected using a parental questionnaire and the innovative collection of Key Stage 1 data to assess educational attainment. The OCS involved no interventions and was a follow-up study only.
Organisational structure

The ORACLE Children Study was funded by the MRC in 2002 and the results were published in September 2008. I was the Chief Investigator for the OCS, and together with the other applicants designed the protocol (Appendix three). The other investigators were Professor David Taylor (Obstetrician), Professor Peter Brocklehurst (Director NPEU), Professor Neil Marlow (Neonatologist), Dr Alison Salt (Community Paediatrician) and Professor David Jones (Statistician). These investigators formed the Project Management Group (PMG). Each investigator brought their area of expertise; I was lead researcher with responsibility for the day to day organisation and coordination of the study. The study was based at the University of Leicester and at its height eight members of staff were employed. During the first 18 months PMG met three times and thereafter annually to review progress.

Design of the ORACLE Children Study

The follow-up of the children born to mothers who had participated in ORACLE began in the summer of 2002. During the first 18 months a feasibility study was undertaken which showed, first, that the whereabouts of the women and children could be reliably established to enable follow-up contact and, second, that they were prepared to return a questionnaire about their ORACLE child’s health and development. The main study ran until August 2007, when the last of the children was seven years old.
The study was designed to test whether or not the prescription of perinatal antibiotics improved the children’s health, development and educational attainment at seven years of age. A parental questionnaire was chosen to obtain information about the children as the size of the population made individual assessment both impractical and prohibitively expensive. For this reason well-validated and standardised instruments were used to assess the children where possible.

**Primary outcomes**

The primary outcome was defined as the presence of any level of functional impairment (severe, moderate or mild) derived from the Multi-Attribute Health Status (MAHS) using the HUI (Health Utilities Index) Mark III classification system. This was developed to assess the health status of a normal population of children. The questionnaire assesses the level of functional impairment within the attributes of vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain.\(^43\) Each attribute had either 5 or 6 defined levels of impairment, ranging from normal function to severe dysfunction. Each attribute is classified into none, mild, moderate or severe levels of severity for the individual attributes from the standard algorithms available within the HUI coding/procedure manual. The overall level of functional impairment for children was determined by their worst score on any attribute. Sensitivity analyses were also undertaken based on the HUI3 multi-attribute utility scores of overall health-related quality of life\(^44\) (HRQL) which became available after OCS commenced.
Secondary outcomes

Secondary outcomes were: the presence of three or more abnormal attributes derived from the MAHS classification system and the degree of functional impairment (severe, moderate, mild, none) within the individual domains; the number of deaths between trial entry and discharge and age seven years; overall and subscale scores derived from the parent-completed Strengths and Difficulties Questionnaire\textsuperscript{45} (SDQ); the frequency of specific medical conditions including central nervous system problems (cerebral palsy, fits/seizures, hydrocephalus with a shunt), respiratory problems\textsuperscript{46} (wheezing, medication for asthma), hospital admission (both in the last year and for chest problems), diabetes, bowel disorders and developmental problems (Attention Deficit Hyperactivity Disorder (ADHD) derived from the SDQ\textsuperscript{47} or parent report), and other development problems.

Educational attainment: The National Curriculum Tests for reading, writing and mathematics (Key Stage 1 – KS1) undertaken at 7 years of age in England were used to assess all eligible OCS children\textsuperscript{48}. KS1 level data were provided anonymously by the Department for Children, Schools and Families (DCSF), categorised by treatment group.

Planned analysis

Having learned from the ORACLE trial experiences, plans were made for expertise to be available to support the appropriate analysis. This stated that
the size of the study was predefined by the number of women recruited to the ORACLE trial. The indicative power calculation in the protocol noted that about 4500 children were expected to be eligible for the follow-up study from either group. Approximately 3.1% of the children in the ‘any erythromycin’ group were expected to have 3 or more abnormal attributes using the MAHS scale. Assuming an 85% response rate, this gave 80% power (with alpha = 0.05 (two tailed)) to detect a prevalence of 3 or more abnormal attributes in the ‘no erythromycin’ group of 5% (a relative difference between the two groups of 38%) and suggested it would be worthwhile to proceed with the follow-up.

Similarly, a plan of the statistical analyses was presented which was more appropriate to the factorial design of the original trial. Odds ratios (OR) with 95% confidence intervals (CIs) were presented for primary and most secondary outcomes in the groups receiving co-amoxiclav (‘Any co-amoxiclav’: either with or without erythromycin) and erythromycin (‘Any erythromycin’: either with or without co-amoxiclav) separately. Logistic models with terms indicating allocation to co-amoxiclav and erythromycin and an interaction term, corresponding to the ORACLE II trial’s factorial design were also fitted.

Subgroup analyses were more clearly specified in the protocol, relating to multiple and singleton pregnancies, and gestational age subgroups used at randomisation (less than 32 weeks gestation and less than 28 weeks gestation).
Challenges encountered

Design of the questionnaire

The primary method of data collection was a questionnaire to parents. The design and content of the questionnaire was pivotal in engaging potential participants and a systematic review was used to aid its development.\textsuperscript{50} Also important was the practical challenge of establishing the parent's current address. We had not been in contact with parents since recruitment to the trial, though we had indicated at this time that we intended to undertake a follow up study. This challenge was overcome when I negotiated our becoming the first researchers to gain access to National Strategic Tracing Service, which provided current address and GP for participants.

I also designed the structured framework for contact with parents so that the questionnaire arrived in a timely manner and ensured all eligible participants were contacted. This was eventually supported by a comprehensive database. As evidence was not available to predict the impact of a reminder containing a small financial incentive, I designed a small randomised trial to evaluate this. This showed that the response rate, and thus the reliability and validity of the findings, was improved by 11.7\% (95\%CI 4.7\%-18.6\%) with the use of £5 vouchers (\textit{Paper VI}) and these were included to participants with the reminder.

We also designed regular newsletters and a website for parents to maintain interest in the study, and I met a sample of parents annually to gain insights into their requirements.
Collection of educational attainment data

With support from the Qualifications and Curriculum Authority (QCA), we used the National Curriculum Tests (Key Stage 1) undertaken at seven years of age to assess the children’s educational attainment for residents in England. Such tests are not routinely performed in other parts of the UK.

At Key Stage 1 (KS1) all children are awarded a level for each of reading, writing and mathematics. These include levels 4 and 3 which are above average, level 2 (the average level awarded to between 60 and 70% of pupils which is also subdivided in to 3 sub-levels), and “below level 2”, which includes children who attained level 1, who were “working towards level 1” or who were not entered (“disapplied”) by the teacher.

I negotiated permissions for the provision of anonymised KS1 level data through DCSF, categorised by treatment group, as response rates from parents regarding KS1 proved insufficient to generate sufficiently reliable data. As the DCSF data were anonymous, this strategy was acceptable to both the investigators and the Research Ethics Committee. While level scores are arguably rather weak measures of attainment, the analysis of these data on the vast majority of the children increased the reliability and validity of our knowledge of the children’s educational attainment.
The results of the ORACLE Children Study

Some of the results of the ORACLE Children Study proved to be unexpected and challenging. The findings were published in the Lancet in September 2008 (Papers VII and VIII).

Results for children whose mothers had PROM

Outcome was determined for 75% of eligible children. The analysis shows that there was no clear evidence of differences in the proportion of children with any functional impairment following prescription of erythromycin (with or without co-amoxiclav) [OR 0.91 (95% CI 0.79, 1.05)] or co-amoxiclav (with or without erythromycin) [OR 1.11 (0.96, 1.28)]. There were biologically plausible differences found which are consistent with the short term benefits observed in the ORACLE Trial. These include improvement in respiratory function with erythromycin (severe asthma requiring steroid treatment [OR 0.56 (0.35, 0.92)]) and increased bowel disorders with co-amoxiclav [OR 1.71 (1.05, 2.79)] but these results need to be treated with caution due to the multiple comparisons undertaken.

Results for children whose mothers had SPL

Outcome was determined for 71% of eligible children. Overall, prescription of erythromycin (with or without co-amoxiclav) was associated with marginal increases in the proportions of children with any functional impairment [OR 1.18 (1.02, 1.37)]. There was no clear effect with co-amoxiclav (with or without erythromycin) [OR 1.03 (0.89, 1.19)]. No effects were demonstrated on the number of deaths, other medical conditions, behavioural patterns or educational
attainment. However, there was an excess of children who developed cerebral palsy following erythromycin [OR 1.93 (1.21, 3.09)] or co-amoxiclav [OR 1.69 (1.07, 2.67)], although the overall risk of cerebral palsy was low (2.5%).

So, not only did we find no clear improvements at seven years for children whose mothers had PROM but we also found small increases in any functional impairment as well as cerebral palsy in children whose mothers had SPL. In an attempt to explain these findings, we called together a group of world experts (Appendix 4) to explore possible explanations; there did not appear to be an evident explanation on which consensus could be reached by this group.

The results have also been reviewed by a group of experts for the Commission on Human Medicines (CHM). The CHM’s responsibilities include advising the UK government ministers on matters relating to human medicinal products, giving advice in relation to the safety, quality and efficacy of human medicinal products, and promoting the collection and investigation of information relating to adverse reactions for human medicines. They concluded that, there was no reason to change current guidance of giving erythromycin to women with PROM and that as current clinical guidelines do not recommend the use of antibiotics in women with SPL in the absence of evidence of infection, no regulatory action was indicated. CHM advised that the results of the ORACLE Children Study did not have any relevance for the use of antibiotics in pregnancy for women with overt infections and that treatment of infection was essential and often life-saving for both mother and baby. However, the RCOG has not yet indicated when they will review their guidelines in this area.
The papers have benefited from such scrutiny. However I have reflected that this degree of attention might not have happened had the results showed antibiotics to be of benefit, perhaps suggesting a wider bias towards favourable outcomes of medication.

Changes in practice

Whether the results of the OCS will change practice is an interesting question. The study found that for women with PROM, the short term benefits suggested by the original trial have not been translated into longer term ones. It is therefore unclear whether clinicians will continue to prescribe erythromycin for women with PROM. If it is uncertain whether a woman has PROM, clinicians may be more cautious because of the apparent risks found with either antibiotic to children whose mothers had SPL and intact membranes. The findings clearly indicate that antibiotics should not be prescribed for women with SPL and again it will be interesting to determine whether practice is consistent with this.

Among the expert group convened to discuss the OCS findings, opinion varied as to the importance of the reduction in neonatal outcomes found in the original ORACLE trial, with obstetricians feeling they were more important than neonatologists, who of course deal with them routinely. For women with SPL this study adds to the evidence from other randomised studies\textsuperscript{33} that antibiotics are not indicated in women who present in SPL with intact membranes and no evidence of overt infection.
Overt infection can cause maternal and neonatal morbidity and rarely mortality and it was important that the messages were clearly given when the results are published to ensure women who did have overt infection did take their prescribed treatment. To this end the MRC, Medicines and Healthcare products Regulatory Agency (MHRA) and the Department of Health (DH) were involved in publication plans. I also led the plans for the results to be given to participants who have requested them in a timely manner, just before they were published in the Lancet.

Thanks to the huge amount of planning and the involvement of the MRC, DH and MHRA publication of the results seems to have gone smoothly in that they have not been over-interpreted the press and the public health message that antibiotics should be taken if infection is diagnosed has been clear. As far as we can assess at present the impact on participants of receiving these results has been minimal. A Helpline was established for the fortnight following publication and staffed by trained midwives. It received 37 calls (10 from non participants) and to date we have received nine requests from women to know which treatment they received. A more detailed evaluation of the impact of receiving the results leaflet is the subject of further research - see below.

**Summary**

Leading the seven year follow up of the UK children whose mothers joined the original trials has also proved both hugely challenging and rewarding. The results showing no benefit for women with PROM and the risk of harm for women with SPL was unexpected. The discovery of harm was especially challenging, but this discovery is critically important as it may protect future
generations from the risks associated with an intervention that appeared, on the basis of the extant clinical and observational evidence before the trial began, to be plausibly of benefit, and to safe at least. The effects the ORACLE Children Study results will have on clinical practice are not easy to predict, but it is reassuring that the design, conduct, analysis and scientific scrutiny of the findings mean that the results are as reliable and valid as possible. The OCS demonstrates the importance of longer term follow up and the need for dissemination of complex and challenging results to participants.
CHAPTER FOUR: GENERATING THE EVIDENCE

UNDERSTANDING PARTICIPANTS' PERSPECTIVES

Background

There remains a need to access participants’ perspectives and experiences alongside evaluations of the effectiveness of treatments. This has been a complementary theme running throughout both the ORACLE Trial and the Children Study.

My interest in participants’ views is long held. In the early 1980s I worked as a midwife in Obstetric Ultrasound at King’s College Hospital in London, a regional centre for the diagnoses of fetal abnormality. Having previously worked in a hospice caring for terminally ill patients, I did not have some of the reticence of other staff about giving parents bad news or talking about bereavement or death. I identified the enormous distress these parents were experiencing. When I could not identify an appropriate self-help group, I was involved in the beginnings of Antenatal Results and Choices (ARC) which has been in existence for 20 years. The support group provides information and support for parents undergoing antenatal screening and the diagnosis of abnormality, and I was their first Chair and remain one of their advisors. One of the first publications in this area appeared in 1988 (Paper IX).

Consent to trials in critical situations for pregnant women raises particular ethical issues and questions of best practice as decisions involve a third party:
the unborn or new-born baby. I have led a questionnaire study which evaluated participants understanding of the ORACLE trial. Semi-structured interviews were used to explore both participants’ understanding and views of receiving the results of the trial and these are published as two separate papers.

**Understanding of the ORACLE Trial**

*The questionnaire survey*

I aimed to evaluate participants’ understanding of the ORACLE trial using a questionnaire survey which I designed (*Paper X*). The questionnaire was developed following a literature review, consultation with experts in the field and piloting during 1996. It asked about the amount of information women received, whether that was from the leaflet or the clinicians caring for them and which they found most helpful. It also asked if the women had felt under pressure to join the Trial and what they had understood they had joined.

The questionnaire was sent to 3074 women from 55 maternity units between 1996 and 2000. A response rate of 61% (1875/3074) was achieved using a reminder. Written answers were given by 1462 women to a specific question as to why the trial was being carried out. Content analysis suggested that the information leaflet was highly valued by participants as a source of information about the trial. While the research objective (from a trial perspective) was primarily to evaluate the health of the baby, participants’ objectives were to prevent the possible preterm birth. Of the five key facts about the trial described in the information leaflet, 400 (27%) participants reported one key point, 550
(38%) two clear points, 229 (16%) three key points and 23 (1.5%) four clear points. None reported five clear points and it was not possible to classify 46 (3%) of responses. Vague, confused understanding or poor recall were evident in 204 (14%) of responses and 266 (14%) of women reported that they had felt under pressure to join the trial. When explored further by letter with these women, the majority perceived the pressure to arise from their circumstances (including pressure of time and worry) and not the clinicians.

Even through the ORACLE Trial was run as a model of good practice, in that the trial information leaflet had been developed with consumer involvement and staff were trained regarding the trial before they recruited participants, this questionnaire study confirmed that the meaning participants give to research may not be the same as those that the researchers meant them to have.\textsuperscript{51} The conclusions questioned whether it was realistic for participants to demonstrate full or complete understanding of the scientific issues or even understanding of the principles of trial design and suggested that there needed to be a re-evaluation of our expectations of informed consent. They suggested we should be moving towards an emphasis on the provision of information that involves consumers in its design, content and evaluation\textsuperscript{52} rather than an expectation that all participants should demonstrate they are fully informed.

\textit{The interview study}

The ORACLE Trial results were requested by 197 women in the Trent region. These women were asked to either complete a questionnaire or opt for face-to-face interview. We conducted interviews with 20 of the 22 women who agreed
to interviews and explored both understanding of the trial and the impact of receiving the results.

The first paper from the interview study (Paper XI) explored women’s understanding of participation in the ORACLE trial. The study was designed by me, with Mary Dixon-Woods; interviews were undertaken by Kate Windridge. In these interviews women gave prominence to the socio-emotional aspects of the interactions with healthcare professionals in making decisions about trial participation. Their accounts suggested that the stressful nature of the time at which they were recruited (when they were in threatened preterm labour or with PROM) affected their ability to absorb information and that many of them had poor understanding of trial design and practicalities. The main motivation for trial participation was the possibility of an improved outcome for the baby. The participants judged the trial as having little or no risk associated, as antibiotics were perceived as risk free. This highlights the need to pay particular attention to the explanation of risk when evaluating ‘routine’ treatments discussed earlier. This qualitative study concluded, once again, that rigorous governance arrangements, particularly in critical situations, should protect participants as complete understanding of the trial design and processes by participants was probably unrealistic.
Giving results to participants

The ORACLE Trial

How to feed back results of studies to participants an increasingly important question given that feedback to research participants is emphasised as a bioethical principle,53 54 55 and an element of good research practice,56 the Department of Health’s Research Governance Framework (2nd edition) recommends that “findings from [research] work [be] disseminated promptly and fed back as appropriate to participants”.57 The International Ethical Guidelines for Biomedical Research Involving Human Subjects58 specify that offering results to subjects after study completion is an essential obligation of researchers (guideline 6, article 2). Despite the emphasis placed on feedback of results, understanding of how this might be done and the impact on participants is little understood.59

A summary of the results of the ORACLE trial was written with consumer involvement and sent to participants who requested them at the same time as they were published in The Lancet in March 2001. All 8941 women who joined the ORACLE trial were asked if they wanted to receive the results when they were sent a thank you card immediately following participation. When they participated in the questionnaire survey approximately one third were given a second opportunity. However only 20% of participants requested the results of the trial (1803/8941). It may be that many women did not realise what was meant by the question about results or that they were not interested – or were perhaps too busy after having a baby to respond to the thank-you card.
The interviews we conducted with 20 of the 22 women in the Trent region as described earlier (Paper XII) showed that reactions to the results leaflet were generally positive or neutral, but there was some evidence of negative implications for women who had adverse outcomes. What was clear was that women fitted the results to their personal narrative and that they were disappointed to receive a generic summary of results. Women wanted to know their treatment allocation and the implications for their pregnancy. The study recommended further research into the consequences of routinely giving results to participants as it widely advocated \(^{55,58}\) and further exploration of what may be best practice.

**The ORACLE Children Study**

The results of the Children Study could be potentially upsetting/concerning to participants and this raises the question of how they can best be fed back in order to ensure that participants' priorities are addressed, the results are presented clearly in language that is familiar to participants to minimise misunderstanding, and any adverse impacts are minimised. This has offered the opportunity for me to develop, with Mary Dixon-Woods, an evaluation of the feedback of these results to participants. This study is currently underway and will be completed in June 2009. The evaluation comprises four phases, the first two of which are completed: focus groups with OCS participants and the development of a results leaflet which appears in Appendix five.

The third and fourth phases consist of the analysis of the returned questionnaires and semi-structured interviews with approximately 40-45 OCS participants to evaluate the impact of the leaflet and the results. Participants will
be selected purposively based on their responses to the questionnaire and their child’s outcome from the ORACLE Children Study.

Summary

There is little doubt that participants’ perspectives and experiences add insights not obtained through quantitative methods alone. Additional work I have undertaken into informed consent for elective and emergency surgery has also shed light on the fact that the introduction of more complex forms and procedures may not address patients needs, and also highlights the importance of the participant perspective (Papers XIII-XVI)

The work I have undertaken both on the understanding participants have of the research they have joined and of the impact of receiving results has added to the evidence in this area. The better we understand participants’ perspectives the more likely we are to meet their needs and engage in proper cooperative partnerships.
CHAPTER FIVE: SUMMARY AND CONCLUSIONS

Role of antibiotics in preterm birth

Premature birth is associated with personal stress and health problems around birth and with later disabilities among surviving children. These pose challenges for children themselves and their families, but also for public health and education services. My body of work has aimed to make a substantial contribution to research on premature birth. The origins of the ORACLE trial lay in observational evidence that had suggested that subclinical infection might have a role in the causation of both pre-term rupture of membranes (PROM) and spontaneous preterm labour (SPL) with intact membranes and that antibiotics might prolong pregnancy as well as improve neonatal outcomes. The ORACLE Trial (1994-2000) evaluated the use of erythromycin and co-amoxiclav in these circumstances using a factorial design. It remains the largest trial in preterm labour and recruited over 11,000 women, mainly from the UK. The results showed some evidence of benefit associated with the prescription of erythromycin for women with PROM; women are now routinely prescribed erythromycin as a result. While co-amoxiclav was shown to prolong pregnancy, it was also associated with increases in the number of babies with necrotising enterocolitis (and therefore posed risks). For women with SPL, no benefit or harm to babies was seen at discharge from hospital and antibiotics are therefore not indicated when women present with signs of pre-term labour but do not have ruptured membranes.
Further important evidence has also been obtained from the ORACLE Children Study (OCS), which was a long-term follow up of ORACLE trial children. Given the apparently promising outcomes of the ORACLE trial for women with PROM who were prescribed antibiotics, it was perhaps surprising there was no evidence of long-term benefit or harm to children associated with the prescription of either erythromycin or co-amoxiclav. More surprising and disturbing were the results for women with SPL who were prescribed antibiotics. Increases in functional impairment were associated with the prescription of erythromycin, and prescription of either antibiotic was associated with increases in the numbers of children with cerebral palsy. The change in practice that will result from these papers is difficult to predict as the papers have only recently been published.

The study may have a more diffuse but nonetheless extremely important scientific impact. It is the largest follow up of a randomised group of children born to mothers showing signs of giving birth early and is likely to strengthen the argument that short-term outcomes are not sufficient to assess longer term outcomes, and comprehensive longer term follow up of children whose mothers are given interventions in pregnancy is required. The need for more comprehensive, longer, and more detailed follow-up of many other interventions needs to be carefully considered.
**Evaluative and participative approach to trial practice**

My evaluation of recruitment and retention strategies as the trial and the OCS proceeded has allowed generation of fresh evidence about research practices which have added to the evidence available. In overcoming the challenges encountered while running a major, complex trial, the model I developed, where midwives/neonatal nurses play a pivotal role in maternity research, in which they are both acknowledged and valued, has been important and has changed practice in the wider maternity research arena. Similarly, there are important lessons for others about the way I have maintained contact with participants, once again based on available evidence, which resulted in an excellent response rate that has meant we have been able to present results which stress the importance of long term follow up.

My collaborative style of leadership has influenced national policy as I led the National Institute for Clinical Excellence (NICE) Intrapartum Care Guideline. This emphasised the normality of birth for most women, provided clear instances where referral is appropriate and highlighted the importance of good communication (**Paper XVI**).

**Importance of participants’ perspectives**

The qualitative studies and surveys which have explored participants’ views and experiences have also increased understanding and may help in the design and conduct of future studies. It has, in particular, given insights into the need for caution when explaining risk in trials which evaluate ‘routine’ treatments, and the need for care in giving results of studies to participants.
How to explain the risk involved in any research should also be considered carefully. Despite careful training by the ORACLE team, the risks associated with antibiotics in pregnancy may have been perceived by both study participants and clinicians as being minimal, as the treatment being tested was considered routine. However, the antibiotics were being tested outside their normal area and the effect was not known: while evidence suggested there might be benefit, we were uncertain (in clinical equipoise) at the time. The full importance of this issue to the ORACLE Trial and Children Study has only been recognised now that we know the results (harm to those with SPL) and other researchers should bear this in mind when developing information for both participants and clinicians. Future researchers testing ‘routine’ treatments should take an evaluative approach to this area in order to generate evidence that can be used in future studies. My work on consenting to surgery demonstrates that without a rigorously informed approach, there is a danger that laudable ethical aspirations simply become converted into ritualised procedures that do little to engage people properly.

**Changing practice**

There are many stages involved in taking evidence from papers showing results of research into practice actually changing. Clinicians first need to understand research findings to decide whether practice should change. They then need to accept the findings, which can be difficult if they challenge current practice. Implementation is more likely to occur in an environment which embraces
research and change. Finally, with participant approval, evidence based decisions can be made to improve clinical outcomes.

Changing practice presents particular challenges\textsuperscript{28} but it is interesting to reflect on the contrasts between the uptake of the ORACLE findings and a situation where the evidence has been stronger and yet the change in practice slower to achieve. Respiratory distress syndrome (RDS) and its complications are key factors affecting both the mortality and morbidity of preterm babies. Liggins\textsuperscript{61} first observed that lambs exposed to prenatal corticosteroids appeared viable at an earlier gestation than expected in 1969. The first systematic review was undertaken in 1990\textsuperscript{62} and included 11 randomised placebo controlled trials. It showed that antenatal corticosteroids were associated with a 50% reduction in RDS and neonatal death and yet practice was slow to change with only 20-30% of women receiving them by 1993\textsuperscript{63}. Current RCOG guidance updated in 2004\textsuperscript{64} recommends their prescription and there is little doubt that they are widely prescribed now, but this is some 20 years since the evidence first came to light.

In the future we should focus on understanding what influences clinical practice and how best to change it in ways that are consistent with the evidence.
Summary

My desire to improve care to women during pregnancy and birth by generating high quality scientific evidence to inform practice and also exploring participants’ views and understanding has been largely successful, but I have not done so in isolation. While I have led the work, I have been fortunate to develop strong collaborations and to have hugely enjoyed the journey.
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>Attention Deficit Hyperactivity Disorder</td>
</tr>
<tr>
<td>ARC</td>
<td>Antenatal Results and Choices</td>
</tr>
<tr>
<td>CHM</td>
<td>Commission Human Medicines</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>DCSF</td>
<td>Department of Children, Schools and Families</td>
</tr>
<tr>
<td>DH</td>
<td>Department of Health</td>
</tr>
<tr>
<td>ECPC</td>
<td>Effective Care in Pregnancy and Childbirth</td>
</tr>
<tr>
<td>GBS</td>
<td>Group B Streptococcus</td>
</tr>
<tr>
<td>HRQL</td>
<td>Health Related Quality of Life</td>
</tr>
<tr>
<td>HUI</td>
<td>Health Utilities Index</td>
</tr>
<tr>
<td>KS1</td>
<td>Key Stage 1</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
</tr>
<tr>
<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
</tr>
<tr>
<td>MAHS</td>
<td>Multi-Attribute Health Status</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Clinical Excellence</td>
</tr>
<tr>
<td>NPEU</td>
<td>National Perinatal Epidemiological Unit</td>
</tr>
<tr>
<td>NSTS</td>
<td>National Strategic Tracing Authority</td>
</tr>
<tr>
<td>OCS</td>
<td>ORACLE Children Study</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
</tr>
<tr>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>ORACLE</td>
<td>Overview of the Role of Antibiotics in the Curtailment of Labour and Early Delivery</td>
</tr>
<tr>
<td>PMG</td>
<td>Project Management Group</td>
</tr>
<tr>
<td>PROM</td>
<td>Preterm Rupture Of the Membranes</td>
</tr>
<tr>
<td>RDS</td>
<td>Respiratory Distress Syndrome</td>
</tr>
<tr>
<td>RR</td>
<td>Relative Risk</td>
</tr>
<tr>
<td>QCA</td>
<td>Qualifications and Curriculum Authority</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
</tr>
<tr>
<td>RDS</td>
<td>Respiratory Distress Syndrome</td>
</tr>
<tr>
<td>RCOG</td>
<td>Royal College of Obstetricians and Gynaecologists</td>
</tr>
<tr>
<td>SIDS</td>
<td>Sudden Infant Death Syndrome</td>
</tr>
<tr>
<td>SPL</td>
<td>Spontaneous Preterm Labour (intact membranes)</td>
</tr>
<tr>
<td>SDQ</td>
<td>Strengths and Difficulties Questionnaire</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
</tbody>
</table>
APPENDICES

Appendix One: List of relevant publications

Appendix Two: ORACLE Trial protocol

Appendix Three: ORACLE Children Study protocol which contains the parental questionnaire

Appendix Four: Composition of Expert Group

Appendix Five: ORACLE Children Study results leaflet for participants
Appendix One:

List of relevant publications

*The ORACLE Trial*


The ORACLE Children Study


**Understanding participants' perspectives**


**Collaborative leadership style**

The ORACLE Trial

Paper I:

Kenyon S, Taylor DJ, Tarnow-Mordi W for the ORACLE Collaborative Group.

Broad-spectrum antibiotics for preterm, prelabour rupture of the fetal membranes: the ORACLE I randomised Trial.

Lancet; 2001; 357: 979-988.

Contributions:

Sara Kenyon, David Taylor, Richard Peto and William Tarnow Mordi designed the study protocol. David Taylor and Sara Kenyon supervised the study. Sara Kenyon and the trial team took responsibility for the day to day contact with the centres, the organisation of the drug supplies, and the management of the data. The statistical analysis was done by Ann Blackburn, supported by Richard Peto.
PAGES REMOVED

Full text can be consulted in the David Wilson Library, University of Leicester.
The ORACLE Trial

Paper II:

Kenyon S, Taylor DJ, Tarnow-Mordi W for the ORACLE Collaborative Group.

Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomised Trial.


Contributions:

Sara Kenyon, David Taylor, Richard Peto and William Tarnow Mordi designed the study protocol. David Taylor and Sara Kenyon supervised the study. Sara Kenyon and the trial team took responsibility for the day to day contact with the centres, the organisation of the drug supplies, and the management of the data. The statistical analysis was done by Ann Blackburn, supported by Richard Peto.
Full text can be consulted in the David Wilson Library, University of Leicester.
The ORACLE Trial

Paper III:

Kenyon S, DJ Taylor

The effect on clinical practice of the publication of a major clinical trial in a high impact journal – The ORACLE Trial experience.


Contributions:

Sara Kenyon designed the study and supervised the data collection and entry. Both authors viewed the results and contributed to the paper.
Full text can be consulted in the David Wilson Library, University of Leicester.
The ORACLE Trial

Paper IV:

Kenyon S, Boulvain M, Neilson J

Antibiotics for preterm rupture of the membranes: a systematic review.


Contributions:

Sara Kenyon identified the relevant trials, extracted the data and wrote the text of the review. Michel Boulvaine and Jim Neilson checked the extracted data. All authors contributed to the paper.
PAGES REMOVED

- Full text can be consulted in the David Wilson Library, University of Leicester.
The ORACLE Trial

Paper V:

Kenyon S, Rhodes A, Taylor DJ

A recipe for successful recruitment to a randomised controlled trial.


Contributions:

Sara Kenyon conceived the idea for the local midwives and implemented it with support from the David Taylor and Regional Midwives; Rebecca Smyth, Amanda Rhodes, Sarah Cooper and Amanda Wilson. Sara Kenyon and Amanda Rhodes wrote the first draft of the paper. All authors approved the final manuscript.
PAGES REMOVED

- Full text can be consulted in the David Wilson Library, University of Leicester.
The ORACLE Children Study

Paper VI:

Kenyon S, Pike K, Jones D, Taylor D, Salt A, Marlow N, Brocklehurst P

The effect of a financial incentive on return of a postal health and development questionnaire: a randomised trial.


Contributions:

Sara Kenyon and Peter Brocklehurst designed the trial. David Jones and Katie Pike carried out the analysis. Neil Marlow, Alison Salt and David Taylor contributed to the conception, design and interpretation. All authors read and approved the trial manuscript.
PAGES REMOVED

- Full text can be consulted in the David Wilson Library, University of Leicester.
The ORACLE Children Study

Paper VII:

Kenyon S, Pike K, Jones DR, Brocklehurst P, Marlow N, Salt A, Taylor DJ.

Childhood outcomes following the prescription of antibiotics to pregnant women with preterm rupture of the membranes: 7 years follow-up of the ORACLE I trial.


Contributions:

All authors contribute to the study design, developed the protocol, and contributed to the drafting of the paper. Sara Kenyon led the study and together with David Taylor and Peter Brocklehurst contributed knowledge of maternity practice. Katie Pike and David Jones provided statistical knowledge: Neil Marlow and Alison Salt contributed knowledge on childhood outcomes.
Full text can be consulted in the David Wilson Library, University of Leicester.
The ORACLE Children Study

Paper VIII:

Kenyon S, Pike K, Jones DR, Brocklehurst P, Marlow N, Salt A, Taylor DJ.

Childhood outcomes following the prescription of antibiotics to pregnant women with spontaneous preterm labour: 7 years follow-up of the ORACLE II trial.


Contributions:

All authors contribute to the study design, developed the protocol, and contributed to the drafting of the paper. Sara Kenyon led the study and together with David Taylor and Peter Brocklehurst contributed knowledge of maternity practice. Katie Pike and David Jones provided statistical knowledge: Neil Marlow and Alison Salt contributed knowledge on childhood outcomes.
Full text can be consulted in the David Wilson Library, University of Leicester.
Understanding participants’ perspectives

**Paper IX:**

Kenyon S, Hackett G A, Cambell S

Termination of pregnancy following diagnosis of fetal malformation: the need for improved follow-up services.

Clinical Obstetrics and Gynaecology, 1988; 31; 1: 97-100.

**Contributions:**

Sara Kenyon conceived the study and carried out the interviews. Gerald Hackett wrote the paper together with Sara Kenyon. All authors contributed to the chapter.
Full text can be consulted in the David Wilson Library, University of Leicester.
**Understanding participants’ perspectives**

**Paper X:**

Kenyon S, Dixon-Woods M

What do they know? a content analysis of women’s perceptions of trial information.


**Contributions:**

Sara Kenyon conceived the study, conducted the literature review, devised the questionnaire, and supervised its administration. Sara Kenyon and Mary Dixon-Woods devised the coding system. Both authors devised the coding system and drafted the paper.
Understanding participants’ perspectives

Paper XI:


Participating in a trial in a critical situation: a qualitative study in pregnancy.


Contributions:

Sara Kenyon and Mary Dixon-Woods were responsible for the concept and design. Kate Windridge was responsible for the data collection. Mary Dixon-Woods, Sara Kenyon and Clare Jackson were responsible for the data analysis. Mary Dixon-Woods and Clare Jackson wrote the first draft of the paper. All authors interpreted the data, helped with the preparation and approved the manuscript.
Full text can be consulted in the David Wilson Library, University of Leicester.
Understanding participants’ perspectives

Paper XII:

Dixon-Woods M, Jackson C, Windridge K, Kenyon S

Receiving a summary of the results of a trial in pregnancy: Qualitative study of participants’ views.


Contributions:

Sara Kenyon and Mary Dixon-Woods were responsible for the concept and design. Kate Windridge was responsible for the data collection. Mary Dixon-Woods, Sara Kenyon and Clare Jackson were responsible for the data analysis. Mary Dixon-Woods and Clare Jackson wrote the first draft of the paper. All authors interpreted the data, helped with the preparation and approved the manuscript.
PAGES REMOVED

- Full text can be consulted in the David Wilson Library, University of Leicester.
Understanding participants’ perspectives

**Paper XIII:**

Akkad A, Jackson C, Kenyon S, Dixon-Woods M, Taub N, Habiba M.

Informed consent for elective and emergency surgery: questionnaire study.


**Contributions:**

Marwan Habiba, Mary Dixon-Woods, Andrea Akkad and Sara Kenyon conceived and designed the study, and obtained funding. Marwan Habiba, Sara Kenyon, Clare Jackson, Mary Dixon-Woods and Andrea Akkad deigned and piloted the questionnaire. Clare Jackson undertook administration of the survey, data entry and preliminary analysis. Andrea Akkad and Nick Taub undertook the analysis. All authors contributed to the paper.
PAGES REMOVED

- Full text can be consulted in the David Wilson Library, University of Leicester.
Understanding participants’ perspectives

Paper XIV:

Habiba M, Jackson C, Akkad A, Kenyon S, Dixon-Woods M.

Women’s account of consenting to surgery: is consent a quality problem?


Contributions:

Marwan Habiba, Mary Dixon-Woods, Andrea Akkad and Sara Kenyon conceived and designed the study, and obtained funding. Marwan Habiba, Sara Kenyon, Clare Jackson, Mary Dixon-Woods and Andrea Akkad designed and piloted the questionnaire. Clare Jackson undertook administration of the survey, data entry and preliminary analysis. Andrea Akkad and Nick Taub undertook the analysis. All authors contributed to the paper.
Full text can be consulted in the David Wilson Library, University of Leicester.
Understanding participants’ perspectives

Paper XV:

Akkad A, Jackson C, Kenyon S, Dixon-Woods M, Taub N, Habiba M.

Patients’ perceptions of written consent: questionnaire study.


Contributions:

Marwan Habiba, Mary Dixon-Woods, Andrea Akkad and Sara Kenyon conceived and designed the study, and obtained funding. Marwan Habiba, Sara Kenyon, Clare Jackson, Mary Dixon-Woods and Andrea Akkad deigned and piloted the questionnaire. Clare Jackson undertook administration of the survey, data entry and preliminary analysis. Andrea Akkad and Nick Taub undertook the analysis. All authors contributed to the paper.
PAGES REMOVED

- Full text can be consulted in the David Wilson Library, University of Leicester.
Collaborative leadership style

Paper XVI:

Kenyon S, Ullman R, Mori R, Whittle M. Intrapartum Care.

Care of healthy women and their babies during childbirth. Summary of NICE Guidance.


Contributions:

All authors contributed to reviewing the evidence and writing and correcting the article. SK wrote the paper, which was commented on by the other authors.
PAGES REMOVED

- Full text can be consulted in the David Wilson Library, University of Leicester.
Appendix Two:

ORACLE Trial protocol
Full text can be consulted in the David Wilson Library, University of Leicester.
APPENDIX 3 Copy of the Parent’s Information Leaflet.

The ORACLE Study

Thank you for reading this leaflet at such a difficult time. This hospital like many others in this country and around the world, is currently involved in a study to try to find out if antibiotics can delay premature birth.

This is an invitation to women, like yourself, who have premature contractions or broken waters to ask you to consider joining this study.

You cannot join the study if:
- You are allergic to penicillin
- or if you are taking antihistamines which contain Terfenadine (e.g. Triludan/Seldane) or Astemizole (e.g. Hismanal). These can be taken for hayfever or other allergies.

What is the Study About?

Although the outlook for premature babies has improved in recent years, they are still more likely to have problems which require intensive care such as: short term breathing problems, feeding difficulties, infections or long term development problems. Whatever happens it is often a traumatic and upsetting experience for women and their families.

Some premature contractions or broken waters can be due to a mild unnoticed infection in the membranes surrounding the baby. Although trying to treat the infection with antibiotics might cure it and reduce the risk of premature birth, the antibiotics may have no effect or it might be too late for them.

This study is investigating whether two antibiotics (Augmentin and erythromycin*) commonly used to treat pregnant women and their babies for infection can prevent premature birth. If you decide to join the study you will be given two bottles of tablets. These tablets are both to be taken four times a day for 10 days or until the birth of your baby, whichever comes first. The bottles either contain antibiotics or dummy tablets. Which tablets you get will be decided by chance, neither you or your doctor will know what you are taking. This information will be kept at another hospital and can be obtained if your doctor needs to know.

As you may know, taking an antibiotic may have side effects for some people. These are usually mild and short lasting. Antibiotics can make some people feel sick, vomit or have diarrhoea and occasionally cause skin rash, allergy or ‘thrush’. Extremely rarely a temporary jaundice in women can develop (about 1 in 50,000).

There will be no extra tests or hospital visits for either you or your baby. When your baby is born, some information will be collected about your birth and your baby and kept for confidential analysis. We will also be asking some women their views about the study by sending them a questionnaire.

If You Decide to Join the Study

You will be asked to sign a consent form and given two bottles of tablets to take. Whether you decide to join the study or not is for you to choose and this decision will not affect your care. If you have any further questions do ask your doctor or midwife.

Thank you again.

Please contact Sara Kenyon,
Department of Obstetrics, Leicester Royal Infirmary, Leicester if you ever have any queries or comments.

* Augmentin is manufactured by SmithKline Beecham - amoxycillin 250mg and clavulanic acid 125 mg. Erythromycin is manufactured by Parke-Davis Erymax 250 mg. Neither drug is specially licensed for pregnancy, but the Medicines Control Agency have registered their use in this study.
After reading the Parent's Information Leaflet, I have no more questions now and am willing to be given the research medicines on the understanding that I can, if I wish, stop taking them at any time without giving a reason and without this affecting my usual medical care.

Mother's signature
(Please use ball point pen)

Surname:
First name(s):
Woman's birth date: day  month  year
Hospital record No.:

Woman's address:

Please check that EVERY line is completed

Gestational age:  weeks  days
Expected Date of Delivery (EDD)  day month year
Cervical dilatation(cm(s):  (NK if not known)
Prelabour ruptured membranes Yes No
Preterm labour: Yes No
Will the woman definitely get, or has she had in the last week, any of the following drugs?

A: CORTICOSTEROIDS Yes No
B: BETA-AGONISTS Yes No
C: INDOMETHACIN Yes No
D: NIFEDIPINE Yes No
E: OTHER DRUG OR DRUG TRIAL: Specify:

Person completing this form:
Date of entry into the trial  day month year
Name of hospital:  

Please check that you have not missed ANY part of this form
Now mail the top copy of this form in the FREEPOST envelope or any envelope (no stamp required) to:
ORACLE Clinical Co-ordinating Centre, Freepost (LE6283), PO Box 65, Leicester, LE2 7ZR.
Place the bottom copy in the woman's notes.

NOW FOLLOW INSTRUCTIONS LISTED INSIDE THE STUDY DRUG PACK

OS/SE/2/1095

20
Copy of ORACLE Outcome Form

At ENTRY to the study, record mother’s name and DOB here and put this blank form into the notes for postnatal completion.

To be completed on transfer home of the mother after delivery

Person completing this form: ____________________________
Name of hospital: ____________________________

Do you suspect any major adverse reaction to the study drugs? Yes □ No □
If YES, you should telephone the Clinical Coordinating Centre on 0116 2523296
Since delivery has the mother been prescribed any antibiotic treatment for infection? Yes □ No □
(Do not include routine antibiotic therapy for Caesarean section (CS))
If YES, for what? CS wound infection □ Perineal infection □ Uterine infection □ UTI □
Breast infection □ Other □, specify site:
Date mother discharged home (day/month/year):

Baby details: Complete ONE unit per baby - if more than twins give same information on the back of this form for each subsequent baby

BABY 1

Baby’s surname (if different from mother): ____________________________
DOB: ______/______/______ Sex: Girl □ Boy □ Uncertain □ Birthweight: ______ gms
Mode of delivery: Spontaneous vaginal □ Forceps/Ventouse □ Vaginal breech □ Caesarean section □
Status at birth: Liveborn and survived □ Liveborn but died □ No sign of life at birth (stillborn) □
Date of death: ______/______/______ Was a post mortem requested? Yes □ No □

& likely cause:
Is baby being discharged home with mother? Yes □ No □
Was baby admitted to NICU/SCBU/Nursery? Yes □ No □
If YES, name of hospital that the NICU/SCBU is in:

BABY 2

DOB: ______/______/______ Sex: Girl □ Boy □ Uncertain □ Birthweight: ______ gms
Mode of delivery: Spontaneous vaginal □ Forceps/Ventouse □ Vaginal breech □ Caesarean section □
Status at birth: Liveborn and survived □ Liveborn but died □ No sign of life at birth (stillborn) □
Date of death: ______/______/______ Was a post mortem requested? Yes □ No □

& likely cause:
Is baby being discharged home with mother? Yes □ No □
Was baby admitted to NICU/SCBU/Nursery? Yes □ No □
If YES, name of hospital that the NICU/SCBU is in:

Now mail the top copy of this form in the FREEPOST envelope or any envelope (no stamp required) to: ORACLE Clinical Coordinating Centre, Freepost (LE6283), PO Box 65, Leicester, LE2 7ZR. Place the bottom copy in the mother’s notes.

OS/GDC/21/155
Dear

Name of mother: & her date of birth:

Surname of baby (if different): & date of birth:

Please complete the rest of this form, describing what happened to the child in the NICU/SCBU and return it to me. Thank you very much.

Sara Kenyon, Coordinator, ORACLE Trial

Please PRINT using a BALL point pen

To be completed when baby has been discharged from NICU/SCBU

Any adverse event possibly related to antenatal antibiotics? Yes No
Jaundice other than jaundice of prematurity? Yes No

If YES, specify type and cause:

Date of admission to NICU/SCBU/Nursery (d/m/y) / /
Birthweight: grams

Did any blood culture grow organisms considered indicative of clinical infection? Yes No Not done

Was baby given respiratory support by ET tube after admission to NICU/SCBU? Yes No

Total days on ventilator:

Did baby have respiratory distress syndrome confirmed by chest X-ray? Yes No

Was baby given exogenous surfactant? Yes No

Has baby had supplementary oxygen? Yes No

If Yes, please give date last known to have received it: (d/m/y) / /

Did baby receive any cerebral ultrasound scans (see chart on reverse of form)? Yes No

If Yes, did one or more scans show:

Any intraparenchymal cerebral bleed? Yes No

Hydrocephalus ("ventricular index" >4mm above 97th centile)? Yes No

Any parenchymal cyst(s) (Porencephalic cysts or cystic leukomalacia)? Yes No

Did baby have necrotising enterocolitis? Yes No

Proven by x-ray/operation Suspected

Did baby die? Yes No Was post mortem requested? Yes No

If died, date of death: (d/m/y) / /

Likely cause:

If No, date of discharge from this hospital: (d/m/y) / /

If transferred elsewhere, name of hospital & city:

Person completing this form

Please mail the top copy of this form in the FREEPOST envelope or any envelope (no stamp required) to: ORACLE Clinical Co-ordinating Centre, Freepost (LE6283), PO Box 65, Leicester, LE2 7ZH. Place the bottom copy in the baby’s notes.

Thank you

OSFG/21195
REFERENCES


Management Group

David J Taylor  
Professor of Obstetrics and Gynaecology, University of Leicester, U.K.

Sara Kenyon  
Department of Obstetrics and Gynaecology, University of Leicester, U.K.

William Tarnow-Mordi  
Reader in Neonatal Medicine and Perinatal Epidemiology, University of Dundee, U.K.

Richard Peto  
Professor of Medical Statistics and Epidemiology, CTSU, Radcliffe Infirmary, Oxford, U.K.

Steering Committee

Richard Lilford  
Professor of Obstetrics & Gynaecology, University of Warwick, U.K.

Chairman

Senga Bond  
Director of the Centre for Health Services Research, The University of Newcastle Upon Tyne, U.K.

Diana Elbourne  
Acting Director, Perinatal Trials Service Unit, Radcliffe Infirmary, Oxford, U.K.

Barbara Farrell  
Senior Clinical Trials Coordinator, N.T.U., University of Edinburgh, U.K.

Henry Halliday  
Professor of Neonatal Paediatrics, Royal Maternity Hospital, Belfast, U.K.

Sara Kenyon  
Midwife, Department of Obstetrics & Gynaecology, University of Leicester, U.K.

Naren Patel  
Consultant Obstetrician, Ninewells Hospital, Dundee, U.K.

Richard Peto  
Professor of Medical Statistics and Epidemiology, CTSU, Radcliffe Infirmary, Oxford, U.K.

Christopher Redman  
Professor of Obstetric Medicine, John Radcliffe Hospital, Oxford, U.K.

William Tarnow-Mordi  
Reader in Neonatal Medicine and Perinatal Epidemiology, University of Dundee, U.K.

David J Taylor  
Professor of Obstetrics & Gynaecology, University of Leicester, U.K.

Data Monitoring Committee

Adrian Grant  
Director, Health Services Research Unit, University of Aberdeen, U.K.

Chairman

Forrester Cockburn  
Professor of Child Health, Queen Mother’s Hospital, Glasgow, U.K.

Richard Gray  
Principal Scientist, CTSU, Radcliffe Infirmary, Oxford, U.K.

Charles Rodeck  
Professor of Obstetrics and Gynaecology, University College Hospital, London, U.K.

Advisory Group

Patricia Crowley  
Consultant Obstetrician, Coombe Lying-in Hospital, Dublin, Eire

Peter Davey  
Reader in Clinical Pharmacology and Infectious Diseases, University of Dundee, U.K.

Charles Florey  
Professor of Epidemiology & Public Health, University of Dundee, U.K.

Peter Howie  
Professor of Obstetrics & Gynaecology, University of Dundee, U.K.

James King  
Associate Professor of O & G, Mater Misericordiae Mothers Hospital, Brisbane, Australia

Paul Lewis  
Academic Head of Midwifery & Women’s Health, University of Bournemouth, U.K.

Mo Malek  
Reader in Health Policy, Planning and Management, University of St. Andrews, U.K.

Gabriella Phillips  
Consultant Microbiologist, Ninewells Hospital, Dundee, U.K.

Sue Maguire  
Research and Information Group, National Childbirth Trust, London, U.K.

Joe Richards  
Senior Clinical Pharmacist, Ninewells Hospital, Dundee, U.K.

Steve Walkinshaw  
Consultant in Fetomaternal Medicine, Liverpool Maternity Hospital, Liverpool, U.K.

Phil Steer  
Professor of Obstetrics & Gynaecology, Chelsea and Westminster Hospital, London, U.K.
Suspected or Definite Preterm labour or Preterm Rupture of Membranes – then consider:

**Eligibility**

- Women under 37 weeks pregnant with either:
  - Suspected or Definite Preterm labour or
  - Pre-labour rupture of the membranes (can be both)
  - Substantial uncertainty as to whether antibiotics should be prescribed.
  - The Study 'Piggy backs' onto your normal care

**EXCLUSIONS:** either antibiotics already being given, or thought for any reason to be needed or definite reasons not to give antibiotics,
- immediate delivery thought to be desirable or unstoppable
- not premature enough for delivery to cause concern
- other contraindications are specified by doctor's judgment, in accordance with data sheets for both antibiotics, and might include a history of any antibiotic allergy, jaundice, or use of drugs such as theophylline, carbamazepine, digoxin, disopyramide. Also any woman taking either terfenadine (e.g. Triludan/Seldane) or astemizole (e.g. Hismanal) antihistamines available from pharmacists

**Consent**

- Women considered eligible should be given a “Parent’s Information” leaflet, found loose inside the Study Drug Packs on the labour ward.

**Randomisation (study entry)**

- Randomisation is by sequential Study Drug Pack and so it is not necessary to make a phone call
- Single sided Entry Form to complete

**Treatment**

**There are four possibilities:** Augmentin, erythromycin, both, or neither. They all look the same. All Drug Packs contain a ROUND bottle of pills and a SQUARE bottle of pills that are BOTH to be taken qds over the next 10 days (or until delivery).

- **Round bottle:** Augmentin (375 mg qds) or placebo
- **Square bottle:** Erythromycin (250 mg qds) or placebo

If the mother is discharged, give her the rest of the pills to finish at home.

**After Delivery**

- Single-sided Outcome Form completed after the mother is transferred home.
- For those babies who go into SCBU or NICU, another single-sided form will be sent asking for a few details from the notes.

No more forms or follow-up

If UNBLINDING is required urgently contact: 0116 2541414

For all enquiries, reporting of serious adverse events and supplies of study materials contact:

**ORACLE Clinical Co-ordinating Centre, Department of Obstetrics, Clinical Sciences Building, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7ZR**

Tel: 0116 2523296 Fax: 0116 2523154
Appendix Three:

ORACLE Children Study protocol

and the parental questionnaire
PAGES REMOVED

- Full text can be consulted in the David Wilson Library, University of Leicester.
ORACLE Children Study

Questionnaire

Please tell us your name: 

What is your relationship to the child: 

The questions in this form ask about your child’s usual health and usual ability to do things. Please do not report temporary or occasional problems. For example we are interested in how well your child is usually able to get around, talk and see. We will be asking about other things too, like emotions, and ability to learn and remember as well as questions about your child’s health.

You may think that some of the things we ask don’t apply to your child, but we are interested in the overall health of a large group of children. Therefore we need to ask the same questions for each child. If you need any help filling this in do ring us on 0116 252 5813 or email queries to oracle@le.ac.uk.

There are no right and wrong answers! All we want is your opinion about your child’s health. Can you please tick the relevant box below.
Part One: Your child’s ability

1*. Which one of the following best describes your child’s usual ability to see well enough to read ordinary newsprint?

☐ Able to see well enough without glasses or contact lenses
☐ Able to see well enough with glasses or contact lenses
☐ Unable to see well enough with glasses or contact lenses
☐ Unable to see at all

If your child has a problem with seeing, do you know the cause?

☐ Yes ☐ No

If yes, can you please tell us what it is? _________________________________

2*. Which one of the following best describes your child’s usual ability to see well enough to recognise a friend on the other side of the street?

☐ Able to see well enough without glasses or contact lenses
☐ Able to see well enough with glasses or contact lenses
☐ Unable to see well enough with glasses or contact lenses
☐ Unable to see at all

3*. Which one of the following best describes your child’s usual ability to hear what is said in a group conversation with at least three other people?

☐ Able to hear what is said without a hearing aid
☐ Able to hear what is said with a hearing aid
☐ Unable to hear what is said even with a hearing aid
☐ Unable to hear what is said, but do not wear a hearing aid
☐ Unable to hear at all

If your child has a problem with hearing, do you know the cause?

Yes ☐ No

If yes, can you please tell us what it is? _________________________________
4*. Which one of the following best describes your child’s usual ability to hear what is said in a conversation with one other person in a quiet room?

☐ Able to hear what is said without a hearing aid
☐ Able to hear what is said with a hearing aid
☐ Unable to hear what is said even with a heating aid
☐ Unable to hear what is said, but do not wear a hearing aid
☐ Unable to hear at all

5*. Which one of the following best describes your child’s usual ability to be understood when speaking his/her own language with people who do not know them?

☐ Able to be understood completely
☐ Able to be understood partially
☐ Unable to be understood
☐ Unable to speak at all

6*. Which one of the following best describes your child’s usual ability to be understood when speaking with people who know him/her well?

☐ Able to be understood completely
☐ Able to be understood partially
☐ Unable to be understood
☐ Unable to speak at all

7*. Which one of the following best describes how your child usually feels?

☐ Happy and interested in life
☐ Somewhat happy
☐ Somewhat unhappy
☐ Very unhappy
☐ So unhappy that life is not worthwhile

8*. Which one of the following best describes your child’s usual level of pain and discomfort?

☐ Free of pain and discomfort
☐ Mild to moderate pain or discomfort that prevents no activities
☐ Moderate pain or discomfort that prevents a few activities
☐ Moderate to severe pain or discomfort that prevents some activities
☐ Severe pain or discomfort that prevents most activities

* Copyright Health Utilities Inc. (HUInc), 2000
9*. Which one of the following best describes your child's usual ability to walk?

Note: Walking equipment refers to mechanical supports such as braces, a cane, crutches or a walker.

☐ Able to walk around the neighbourhood without difficulty, and without equipment
☐ Able to walk around the neighbourhood with difficulty, but does not require walking equipment or the help of another person
☐ Able to walk around the neighbourhood with walking equipment, but without the help of another person
☐ Able to walk only short distances with walking equipment, and requires a wheelchair to get around the neighbourhood
☐ Unable to walk alone, even with walking equipment. Able to walk short distance with the help of another person, and requires a wheelchair to get around the neighbourhood
☐ Unable to walk at all

If your child has a problem with getting around, do you know the cause?

☐ Yes ☐ No

If yes, can you please tell us what it is?________________________________________

10*. Which one of the following best describes your child's usual ability to use hands and fingers?

Note: Special tools refers to hooks for buttoning clothes, gripping devices for opening jars or lifting small items, and other devices to compensate for limitations of hands or fingers.

☐ Full use of two hands and ten fingers
☐ Limitations in the use of hands or fingers, but does not require special tools or the help of another person
☐ Limitations in the use of hands or fingers, independent with use of special tools (do not require the help of another person)
☐ Limitations in the use of hands and fingers, requires the help of another person for some tasks (not independant even with use of special tools)
☐ Limitations in the use of hands or fingers, requires the help of another person for most tasks (not independent even with use of special tools)
☐ Limitations in the use of hands or fingers, requires the help of another person for all tasks (not independent even with use of special tools)

11*. Which one of the following best describes your child's usual ability to remember things?

☐ Able to remember most things
☐ Somewhat forgetful
☐ Very forgetful
☐ Unable to remember anything at all
12*. Which one of the following best describes your child's usual ability to think and solve day to day problems?

☐ Able to think clearly and solve day to day problems
☐ Has a little difficulty when trying to think and solve day to day problems
☐ Has some difficulty when trying to think and solve day to day problems
☐ Has great difficulty when trying to think and solve day to day problems
☐ Unable to think or solve day to day problems

13*. Which one of the following best describes your child's usual ability to perform basic activities?

☐ Eats, bathes, dresses and uses the toilet normally
☐ Eats, bathes, dresses and uses the toilet independently with difficulty
☐ Requires mechanical equipment to eat, bathe, dress or use the toilet independently
☐ Requires the help of another person to eat, bathe, dress or use the toilet

14*. Which one of the following best describes how your child usually feels?

☐ Generally happy and free from worry
☐ Occasionally fretful, angry, irritable, anxious or depressed
☐ Often fretful, angry, irritable, anxious or depressed
☐ Almost always fretful, angry, irritable, anxious or depressed
☐ Extremely fretful, angry, irritable, anxious or depressed; to the point of needing professional help

15*. Which one of the following best describes your child's usual level of pain or discomfort?

☐ Free of pain and discomfort
☐ Occasional pain or discomfort. Discomfort relieved by non-prescription drugs or self-control activity without disruption of normal activities
☐ Frequent pain or discomfort. Discomfort relieved by oral medicines with occasional disruption of normal activities
☐ Frequent pain or discomfort; frequent disruption of normal activities. Discomfort requires prescription narcotics for relief
☐ Severe pain or discomfort. Pain not relieved by drugs and constantly disrupts normal activities

* Copyright Health Utilities Inc. (HUIInc), 2000
Part Two: Your child's general development

16*. For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of your child's recent behaviour over the last month.

<table>
<thead>
<tr>
<th></th>
<th>Not True</th>
<th>Somewhat True</th>
<th>Certainly True</th>
</tr>
</thead>
<tbody>
<tr>
<td>Considerate of other people's feelings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restless, overactive, cannot stay still for long</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Often complains of headaches, stomach-aches or sickness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shares readily with other children (treats, toys, pencils etc.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Often has temper tantrums or hot tempers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rather solitary, tends to play alone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generally obedient, usually does what adults request</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Many worries, often seems worried</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helpful if someone is hurt, upset or feeling ill</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constantly fidgeting or squirming</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has at least one good friend</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Often fights with other children or bullies them</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Often unhappy, down-hearted or tearful</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generally liked by other children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easily distracted, concentration wanders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous or clingy in new situations, easily loses confidence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kind to younger children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Often lies or cheats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Picked on or bullied by other children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Often volunteers to help others (parents, teachers, other children)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thinks things out before acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steals from home, school or elsewhere</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gets on better with adults than with other children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has many fears, easily scared</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sees tasks through to the end, good attention span</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

17*. Do you have other comments or concerns relating to your child's general development?
18*. Over the last month, has your child had difficulties in one or more of the following areas: emotions, concentration, behaviour or being able to get on with other people?

- No
- Yes minor difficulties
- Yes definite difficulties
- Yes severe difficulties

If you have answered "yes", please answer the following questions about these difficulties. If "no" then go to question 19.

a*. Do the difficulties upset or distress your child?

- Not at all
- Only a little
- Quite a lot
- A great deal

b*. Do the difficulties interfere with your child’s everyday life in the following areas?

<table>
<thead>
<tr>
<th>Area</th>
<th>Not at all</th>
<th>Only a little</th>
<th>Quite a lot</th>
<th>A great deal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friendships</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classroom learning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leisure activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

c*. Do the difficulties put a burden on you or the family as a whole?

- Not at all
- Only a little
- Quite a lot
- A great deal
19. Your child's school.
Which of the following best describes the sort of school your child is in and type of support they receive? (Please tick one box)

- [ ] My child is in a main stream school
- [ ] My child is in a main stream school with some learning support or additional help
- [ ] My child is in a special class or unit
- [ ] My child is in a special school or pupil referral unit (PRU)
- [ ] My child has home or hospital tuition
- [ ] None of these

Please can you describe what best describes the sort of school your child is in: 

______________________________

Part Three: Your child's health

This part asks particularly about whether your child has any wheezing/asthma, hospital admissions, seizures and some particular problems your child may have. Don't be alarmed by any of these questions. The likelihood is that your child will not have or develop any of these serious problems.

20. In the last 12 months, has your child had any attacks of wheezing?

- [ ] Yes  [ ] No  If no, go to question 22

If yes, can you tell us approximately how frequently?

- [ ] Daily
- [ ] Weekly
- [ ] Monthly
- [ ] Less than monthly

21. In the last 12 months, has your child's sleep been disturbed due to wheezing?

- [ ] Never woken with wheezing
- [ ] Seldom wakes (less than one night per week)
- [ ] Frequently wakes (one or more nights per week)

22. In the last 12 months has your child been given any courses of antibiotics for chest problems?

- [ ] Yes  [ ] Don't know  [ ] No

If yes, can you tell us approximately how many? 

23. In the last 12 months has your child been given any other medicines (not antibiotics) for chest problems?

☐ Yes  ☐ Don’t know  ☐ No  If no go to question 24

If yes, can you tell us what they are from the list below?

<table>
<thead>
<tr>
<th></th>
<th>In the last 12 months</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhalers:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Relievers” Ventolin (blue)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bricanyl (blue)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrovent (green)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmeterol (green)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

please tell us which: ____________________________

<table>
<thead>
<tr>
<th>“Preventers”</th>
<th>Becotide (brown)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmicort (brown)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flixtotide (orange)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

please tell us which: ____________________________

24. In the last 12 months has your child been admitted to hospital for any reason?

☐ Yes  ☐ No  If no go to question 25

If yes, can you tell us the reason and number of admissions?

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number of admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest problems</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Anything else</td>
<td></td>
</tr>
</tbody>
</table>

Can you tell us briefly what these were for?

__________________________________________________________________________

__________________________________________________________________________
25. Has your child ever had any fits, seizures and convulsions?

☐ Yes  ☐ No  If no go to question 26

Please tick one answer which best describes your child's seizures/convulsions now:

☐ Not on prescribed medicines for seizures
☐ On prescribed treatment with no seizures
☐ Has less than 1 seizure/month on prescribed treatment
☐ Has more than 1 seizure/month on prescribed treatment

26. Please tick if your child has any of the following conditions?

Yes

☐ Diabetes
☐ Cerebral palsy
☐ Hydrocephalus with shunt
☐ Gastrostomy
☐ Any other bowel stoma

27. Any other problem for which he/she is under the care of a doctor?

☐ Yes  ☐ No

If yes, can you tell us about this problem and give us the diagnosis if you know it?

________________________________________________________________________
________________________________________________________________________

Part Four: You and home environment

We need to know a little about you and your circumstances and have taken some of these questions from the 2001 census. You may need to tick more than one box.

Home environment
These questions apply to the family at home; by this we mean mum (or partner), or dad (or partner) and brothers and sisters.

28. Does anyone in the family smoke?

☐ Yes  ☐ No

29. Does your house have problems with damp or mould?

☐ Yes  ☐ No

30. Has a doctor ever said that any member of your family has asthma?

☐ Yes  ☐ No
31*. Do you rent or own your accommodation?

- Owner (mortgage)
- Council rented
- Private rented (furnished)
- Private rented (unfurnished)
- Housing society or co-operative
- Tied to occupation
- Other (please describe below)
  
  Reason: ________________________________

32*. What is your ethnic group?

Choose ONE section from A to E, then tick the appropriate box to indicate your cultural background.

A  White
- British
- Irish

B  Mixed
- White and Black Caribbean
- White and Black African
- White and Asian
  Any other Mixed background: ________________________________

C  Asian or Asian British
- Indian
- Pakistani
- Bangladeshi
  Any other Asian background: ________________________________

D  Black or Black British
- Caribbean
- African
  Any other Black background: ________________________________

E  Chinese or other ethnic group
- Chinese
  Any other: ________________________________
If there is anything you would like to tell us about your child's health, please tell us here:

Thank you very much for completing the questionnaire.

Please can you check carefully that you have completed every section.

If you would like a summary of the study findings please tick this box:

Please return it in the prepaid envelope provided to:

MRC ORACLE Children Study
Robert Kilpatrick Clinical Sciences Building
University of Leicester
P O Box 65
Leicester
LE2 7LX
## Appendix four: Composition of expert group

<table>
<thead>
<tr>
<th>Name</th>
<th>Expertise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Martin Whittle (Chair)</td>
<td>Obstetrics</td>
</tr>
<tr>
<td>Dr Alison Bedford Russell</td>
<td>Neonatology</td>
</tr>
<tr>
<td>Professor Philip Bennett</td>
<td>Obstetrics</td>
</tr>
<tr>
<td>Professor Kate Costeloe</td>
<td>Neonatology</td>
</tr>
<tr>
<td>Dr Francis Cowan</td>
<td>Developmental Paediatrics</td>
</tr>
<tr>
<td>Professor Diana Elbourne</td>
<td>Statistics</td>
</tr>
<tr>
<td>Professor Olaf Dammann</td>
<td>Neonatal brain development</td>
</tr>
<tr>
<td>Dr Catherine Elliott</td>
<td>MRC member</td>
</tr>
<tr>
<td>Dr Mike Millar</td>
<td>Microbiologist</td>
</tr>
<tr>
<td>Professor Jane Norman</td>
<td>Obstetrics</td>
</tr>
<tr>
<td>Professor Michael O’Shea</td>
<td>Neonatal brain development</td>
</tr>
<tr>
<td>Professor Max Palmar</td>
<td>Statistics</td>
</tr>
<tr>
<td>Professor Roberto Romero</td>
<td>Preterm birth</td>
</tr>
<tr>
<td>Professor Dieter Wolke</td>
<td>Developmental Psychology</td>
</tr>
</tbody>
</table>
Appendix Five:

ORACLE Children Study results leaflet for participants
PAGES REMOVED

Full text can be consulted in the David Wilson Library, University of Leicester.
REFERENCES


5 Randall T. Thalidomide has 37-year history. *Journal of American Medical Association* 1990: 263:1474


8 Spock B. *Baby and Child Care* 1958 London The Bodley Head

9 Beal S. Sleeping position and SIDS Lancet 1988;2:512


21 King J, Flenady V. Antibiotics in preterm labour with intact membranes in Neilsen JP, Crowther C, Duley L, Hodnett ED, Hofmir J (eds) Pregnancy and Childbirth Module of the Cochrane Database of Systematic Reviews( updated 25.11.97) available in the Cochrane Library (database or disc and CDROM).


30 Royal College of Obstetricians and Gynaecologists. Preterm prelabour rupture of the membranes. 2006 *Green Top Guideline* No 44. London RCOG.


32 Kenyon S, Jones D, Brocklehurst P, Marlow N, Salt A, Taylor DJ. UK survey of antibiotic treatment of women with spontaneous preterm labour or preterm rupture of the membranes. Poster at Perinatal Care Conference. 2008 Harrogate


35 Centres for Disease Control and Prevention of Perinatal Group B Streptococcal Disease. MMWR 2002:51 [No. RR-11,1-23].


38 [www.npeu.ox.ac.uk/boost/](http://www.npeu.ox.ac.uk/boost/)

39 [www.hta.ac.uk/1734](http://www.hta.ac.uk/1734)


47 Cuffe SP, Moore CG, McKeown RE. Prevalence and correlates of ADHD symptoms in the National Health Survey. J Atten Disorder 2005:9; 392-401

48 Qualifications and Curriculum Authority (2007). Key Stage 1 Assessments and reporting arrangements. QCA London


57 Department of Health. Research governance framework for health and social care. 2nd Ed 2005 London DH.

58 [http://www.publications.parliament.uk/pa/cm199900/cmselect/cmsctech/332/0062116.htm](http://www.publications.parliament.uk/pa/cm199900/cmselect/cmsctech/332/0062116.htm)

59 Shalowitz DI, Miller FG Communicating the results of clinical research to participants; Attitudes, practices, and future directions. *PLoS Med* 2008; 5(5)e91.doi:10.1371/journal.pmed.0050091

60 Kulier R, Gee H, Khan K. Five steps from evidence to effect: exercising clinical freedom to implement research findings. *BJOG* 2008; 115:1197-1202.


64 Royal College of Obstetricians and Gynaecologists. Antenatal corticosteroids to prevent respiratory distress syndrome. Green top guideline No 7. RCOG London