The QUOTE Study
Qualitative Understanding of Trial Experience

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy

by Rebecca MD Smyth

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Abstract

Background

This thesis presents the QUOTE (Qualitative Understanding of Trial Experience) Study. The study explored women's views and experiences of participating in a large multi-centre randomised controlled trial - The Magpie Trial. The Magpie Trial was designed to test the hypothesis that in women with pre-eclampsia treatment with magnesium sulphate reduces the risk of eclampsia, and so improves outcome. Women recruited to the Magpie Trial all had sufficiently severe pre-eclampsia to warrant consideration of magnesium sulphate for seizure prophylaxis. They were therefore being recruited at a time when they were likely to be having intensive monitoring, and there was often concern about their health and that of the baby. At present little is known about the experiences of pregnant women recruited to trials, especially when in potentially life-threatening situations. Issues regarding the randomisation of pregnant women to trials have been identified as needing special consideration. The QUOTE Study allowed for exploration of pregnant women's experiences around the time of recruitment to the Magpie Trial.

Aim and Objectives

To increase knowledge of pregnant women's perceptions regarding trial involvement, with the aim of improving design and recruitment procedures in future trials, and hence participant experience.

Methodology

Data concerning participants' experience of taking part in the Magpie Trial were obtained in two ways:

(i) Postal questionnaires: The Magpie Trial involved a follow up study, which aimed to find out whether treatment with magnesium sulphate affects women's longer-term risk of death or serious morbidity. All those who took part in the follow up study (761 women) were sent a questionnaire; a

response was received from 81% (619 women). Three questions included in the postal questionnaire gave women the opportunity to express their views regarding participation in the Magpie Trial.

(ii) Semi-structured interviews: Following completion of the postal questionnaire, a sub-set of the women were offered the opportunity to take part in a semi-structured interview to find out, in more detail, about their experiences of joining the trial. Forty women were selected using a sampling matrix based on their characteristics at trial entry and mother and baby post-natal outcomes. Semi-structured tape-recorded interviews were conducted and transcribed verbatim. A coding scheme was created to identify themes, facilitated by a qualitative computer package.

Results

Overall the findings from the trial experience questions on the postal questionnaire confirmed that the majority (85%) of the women were happy with their participation in the trial. From the semi-structured interviews, it highlighted that there is a need for consent processes to recognise the different circumstances under which consent may be given. Self-interest and trust in the clinician was key to participation. Distinction between research and routine clinical care can be unclear. Women appreciate being informed about trial results and welcomed long-term trial follow-up.

Conclusions

The QUOTE Study advances understanding of the experiences of those participating in randomised controlled trials. As data of the type reported here accumulate, clinicians and researchers will have the opportunity to modify research strategies to reflect actual participants' concerns and needs.

Declaration

No portion of the work referred to in this thesis has been submitted in support of another degree of qualification in this or any other university or institute of learning.

Much of the text describing the Magpie Trial and its follow up study in chapter 1 of the thesis was taken directly from the trial protocols (Magpie Trial Protocol 1998, Magpie Trial Follow Up Study Protocol 2004) and the ensuing results papers (Magpie Trial Collaborative Group 2002, Magpie Trial Follow Up Study Collaborative Group 2007a), Magpie Trial Follow Up Study Collaborative Group (2007b).

The data obtained from questions relating to trial experience that were included in the women's follow up postal questionnaire were analysed as part of this thesis. Professor Lelia Duley (Magpie Trial Clinical Co-ordinator) devised these questions with contribution from Professor Diana Elbourne.

Related publications:

For the following publications I took the lead in the writing:

Smyth RMD, Armstrong N. (2007) Magpie Trial long-tem follow-up in the United Kingdom. Available at www.thelancet.com/collections/pre-eclampsia 369; 13-14

Smyth RMD, Spark P, Armstrong N, Duley L (2008). Magpie Trial in the UK: methods and additional data for women and children at 2 years following pregnancy complicated by pre-eclampsia *(BioMed Central in press)*

Smyth RMD, Duley L, Jacoby A, Elbourne D. Women's experiences of participating in the Magpie Trial in the UK as assessed by a postal questionnaire *(submitted to BJOG)*

For the following publications I was a member of the writing committee; however I did not lead in the writing of these papers:

Magpie Trial Collaborative Group (2002). Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. The Lancet; 359: 1877-90

Magpie Trial Follow Up Study Collaborative Group (2004). The Magpie Trial Follow Up Study: outcome after discharge from hospital for women and children recruited to a trial comparing magnesium sulphate with placebo for pre-eclampsia [ISRCTN86938761]. BMC Pregnancy and Childbirth; 4(5).

Magpie Trial Follow Up Study Collaborative Group (2007a) The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia. Outcome for children at 18 months. BJOG 114 (3) 289-299.

Magpie Trial Follow Up Study Collaborative Group (2007b) The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia. Outcome for women at two years. BJOG 114 (3) 300-309.

Farrell B, Duley L (2007) Doing the undoable: Magpie Trial long-tem follow-up. www.thelancet.com 369; 13-14

Oral presentations:

Smyth RMD, Jacoby A, Elbourne D, Duley L (2004) Methods used to explore women's views of participating in the Magpie Trial. Magpie Trial follow up study results conference at University of Oxford.

Smyth RMD, Jacoby A, Elbourne D (2008) Findings from the QUOTE Study (Qualitative Understanding of Trial Experience) International Confederation of Midwives 28th Triennial Congress, Glasgow June 2008.

Poster presentations:

Smyth RMD, Jacoby A, Elbourne D, Duley L, Farrell B (2004) Methods used to explore women's views of participating in a perinatal randomised trial. British Congress of Obstetrics and Gynaecology, Glasgow.

Awards:

July 2004 - prize awarded for best oral presentation. Methods used to explore women's views of participating in a perinatal randomised trial. Postgraduate Research in Science and Medicine Conference, University of Liverpool.

February 2004 – short-listed for interview for MRC Clinical Research Training Fellowship for PhD (QUOTE Study).

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The work was funded through the MRC Senior Clinical Fellowship awarded to Professor Lelia Duley (Magpie Trial Clinical Co-ordinator and Obstetric Epidemiologist, Institute of Health Sciences, University of Oxford).

I am especially grateful to Professor Duley who was fundamental in the initial development of the QUOTE Study and in furthering my interest in trial participation as well as expanding my skills to carry out the research. Her intellectual advice regarding chapter content was also gratefully received.

I am equally indebted to the intellectual support and creativity provided by my two academic supervisors: Ann Jacoby (Professor of Medical Sociology, Division of Public Health, University of Liverpool) and Diana Elbourne (Professor of Health Care Evaluation, Medical Statistics Unit, London School of Hygiene and Tropical Medicine). Professor Jacoby provided me with particular expertise in qualitative work and closely supervised and developed my writing skills. Professor Diana Elbourne provided subject knowledge relating to participants experiences of joining trials and also statistical supervision. I have been extremely fortunate to have two such supportive supervisors and I thank them both.

I am grateful to all colleagues based at the Magpie Trial Co-ordinating Centre, Institute of Health Sciences, University of Oxford. Special thanks are given to Barbara Farrell (Trial Manager), Patsy Spark (Trial Programmer and

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I was provided with secretarial support (transcribing qualitative tape-recorded interviews) by the School of Reproductive and Developmental Medicine, University of Liverpool. Additional administrative support for the project was provided by staff at the Magpie Trial Co-ordinating Centre, University of Oxford.

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Glossary

Antenatal: before birth

Gestation: pregnancy, approximately 40 weeks from the first day of the last normal menstrual period

Intrapartum: the time between onset of the first stage of labour and the completion of the third stage.

Neonatal: relating to the first four weeks after birth

Placenta: the afterbirth

Postnatal: after birth (not more than 28 days)

Postpartum: relating to the period of a few days immediately after birth labour

Pre-term: less than 37 completed gestational weeks

Stillbirth: birth of a baby that shows no evidence of life at any time later than 24 weeks after conception

Tocolytics medications used to suppress pre-term labour

Chapter 1

Introduction and background to the QUOTE Study

1.1 Introduction

This thesis presents the QUOTE (**Q**ualitative **U**nderstanding **o**f **T**rial **E**xperience) Study. The study explored women's views and experiences of participating in a large multi-centre randomised controlled trial - The Magpie Trial (**MAG**nesium sulphate for **P**revention of **E**clampsia), a randomised trial of prophylactic anticonvulsants for women with severe pre-eclampsia (toxaemia). The Magpie Trial was designed to test the hypothesis that treatment with magnesium sulphate for women with pre-eclampsia reduces the risk of eclampsia, and so improves outcome.

It is undisputed that clinical research is important for the continued development of healthcare provision and the wellbeing of society. With this need comes the moral responsibility for researchers to ensure trials are performed in the most ethical way. To assess the understanding and experience of those participating in trials is one way of working towards this goal. The QUOTE study was designed to explore women's views and experiences of participating in the Magpie Trial. The aim of the QUOTE Study was to determine the women's understanding of the purpose of the Magpie Trial, what their views were about taking part in the trial, and their reasons for joining. It also aimed to find out whether the women felt any pressure to join, as well as to evaluate their views on the written and oral information given to them at the time of recruitment. The issues of understanding the methodology of the trial, in particular the concepts of equipoise, randomisation, and blinding, were also explored.

1.2 Background to the research question

At present little is known about the experiences of pregnant women recruited to trials, especially when in potentially life-threatening situations. Although the benefits and problems of carrying out large randomised trials are often highlighted in the medical press, until recently the impact to the trial

participant remained relatively unknown. Issues regarding the randomisation of pregnant women to trials have been identified as needing special consideration (Mohanna and Tunna 1999, Lupton and Williams 2004). Women undoubtedly feel responsible for the child they carry to the extent that they often modify their habits and lifestyle during pregnancy. Pregnancy may affect their ability to make free choices: they may feel bound to accept interventions that might benefit the unborn child which they would rather decline for themselves, or they may refuse treatment for themselves in case it should harm the baby. Pregnancy does bring extra considerations that researchers must bear in mind when asking women to participate in research (Mohanna 1997).

Reviewing the literature identified some of the problems and difficulties women may face when considering joining a randomised trial whilst pregnant. However, there is a scant amount of research that either focuses on pregnant women as a distinct group, or provides an insight into their unique experiences. Although the published literature goes some way to understanding their complex perspectives, there is also much less focus on understanding the views of those needing to consider joining a trial when in a critical situation at a life-changing time in their lives. It was against this background that the present research question evolved.

1.3 Personal context

Prior to conception of the QUOTE Study the co-ordinators of the Magpie Trial, particularly the clinical co-ordinator Professor Lelia Duley, had an interest in exploring participants' experiences of joining trials and saw the Magpie Trial follow up study as an excellent opportunity to do this. This resulted in three questions relating to the women's trial experience being included in the postal survey conducted as part of the UK component of the follow up study. The interest in trial participation by the co-ordinators of Magpie reflected my own curiosity in wanting to explore the views and experiences of those recruited to trials.

This interest stemmed from 13 years of working as a research midwife in perinatal trials. I have been fortunate to work on two large multi centre randomised controlled trials: the Oracle Trial (**O**verview of the **R**ole of **A**ntibiotics in **C**urtailing **L**abour and **E**arly delivery) and the Magpie Trial. My involvement in both trials was predominately to maximise recruitment and therefore meant liaising with midwives and obstetricians. During these meetings they would talk to me about the difficulties they experienced when recruiting women in clinically complicated situations, and would express concern about approaching women in such stressful situations as preterm labour and pre-eclampsia. Many were worried about the potential conflict between maximising recruitment, and providing adequate information to the women in order for them to make an informed decision. Others clearly share such experiences, as recruiting enough participants in a trial is one of the biggest challenges in clinical research; large multi-centre trials often have to be stopped early due to recruitment targets not being achieved.

Working as both a clinical and research midwife at the same time gave me the fortunate opportunity to recruit women to both the Oracle and Magpie Trials. This practical experience together with having an understanding of the importance of maximising recruitment to trials and appreciating the difficulties some clinicians experienced in doing so was the starting point for my interest in understanding more about the way participants were approached and recruited into trials, and more importantly, what this experience was like for those taking part.

The QUOTE study was devised as a result of my experience of working as research midwife for the Magpie Trial and its UK follow up study. My initial involvement in the Magpie Trial was while the main trial itself was still in progress. It had been recruiting for 12 months and had a further two and a half years to run before completion at the time I joined the study team. I was based in Liverpool, and this meant frequent visits to the co-ordinating centre in Oxford throughout my time working on the trial. The main Magpie Trial was followed by a follow up survey of the women and their children. Involvement in the UK component of the follow up study brought me closer involvement

with the women, their children and families by visiting them in their homes. Listening to the women talk about their experiences of being involved in the Magpie Trial, and sometimes the difficulties they experienced, further fuelled my interest in the issues around trial participation.

During this period I was encouraged to develop further my interest in trial participation as well as expand my own skills necessary to carry out research. The clinical co-ordinator, Professor Lelia Duley, was fundamental in this support. I was given responsibility for analysing the data obtained from the three questions relating to trial experience that were included in the women's follow up postal questionnaire. However, I wanted to explore in a more detailed way the experiences of the women taking part in the Magpie Trial, and was keen to develop a qualitative study that would enable me to do this. Further discussions with Professor Duley led me to Professors Diana Elbourne and Ann Jacoby to talk more about my interests in trial participation, which enabled me to examine in detail my research plans. These meetings were instrumental in facilitating the development and formulation of the research question, and so the QUOTE study began to be developed.

Throughout this journey I felt it was essential to explore more in-depth the women's feelings and perceptions than was possible from the postal questionnaire. Therefore a qualitative approach using semi-structured, in-depth interviews was indicated; and this ultimately formed the main method of data collection for the QUOTE Study. Though the women's responses to the three structured questions included in the Magpie Trial follow up study postal survey do not therefore form the main focus of this thesis, data gained from them are described and analysed within it. The postal survey allowed information to be obtained from a large number (619) of women about their Magpie Trial experience; the semi-structured interviews explored this further with 40 of these women. Analysing the data from the responses to the three questions included in the postal survey relating to the women's experiences complemented the qualitative interview material and the two approaches in combination had the potential to produce data that added to the knowledge

base in a more effective way than using either method of data collection alone.

The Magpie follow up study provided the framework for me to design a study asking women about their experiences of joining the trial. This backdrop enabled both quantitative and qualitative approaches to be used in order to understand better the experiences of those participating in randomised trials. The reporting of these experiences forms the basis of this thesis.

1.4 Background to the QUOTE Study

This section provides the background to the QUOTE Study by presenting a brief description of the Magpie Trial, and its follow up study. Most (78%) women when asked to join the Magpie Trial in the UK were experiencing a severe form of pre-eclampsia. Severe pre-eclampsia can be life threatening for both the woman and her unborn child; therefore many women randomised to the Magpie Trial were extremely ill. In order to appreciate trial experience from the women's perspectives it was thought necessary to consider what the background considerations were for them at the time of recruitment. The section begins with presenting a definition and clinical picture of pre-eclampsia and eclampsia; followed by an overview of the clinical management of a woman with pre-eclampsia. A brief description of the Magpie Trial and its results is then provided, concluding with a description of the UK component of the follow up study and my own involvement.

1.4.1 Pre-eclampsia and eclampsia

Pre-eclampsia

Hypertension (high blood pressure) is a common clinical condition during pregnancy. In the UK, the condition occurs in 10 -15% of all pregnancies (Symonds & Symonds 2004:99). The syndrome pre-eclampsia (toxaemia), a multisystem disorder, is defined as hypertension accompanied by proteinuria (protein in the urine) (NHBPEP 2000); and complicates between 2-8% of pregnancies (WHO 1988). It usually occurs any time from 20 weeks gestation onwards and resolves within 6 weeks of delivery, although blood pressure may remain elevated up to 3 months postpartum (Nelson-Piercy 2006:5). For

women who have hypertension alone, pregnancy outcome is similar to that for women with normal blood pressure. Outcome deteriorates once proteinuria develops (Meher et al 2005).

Eclampsia

Eclampsia may be defined as a convulsion superimposed on pre-eclampsia. Seizures may occur antepartum (38%), intrapartum (18%), or postpartum (44%). More than a quarter of women experience their first convulsion before the development of hypertension and proteinuria (Sibai 2007). The national incidence of eclampsia is 2.7 per 10,000 births, and is associated with a considerably higher morbidity and mortality (Douglas and Redman 1994, Knight 2007). As a third of eclamptic fits occur postpartum, intensive monitoring is required, usually for 48 hrs after delivery. Although eclampsia has been reported beyond this time it is unlikely to be associated with serious morbidity. Blood pressure is frequently at its highest 3-4 days after delivery (Shennan 2004:179).

1.4.2 Definitions of pre-eclampsia

Classification and definitions of pre-eclampsia have, in the past, been controversial (Meher et al 2005). More recently there has been a move towards agreeing standard definitions, and ensuring they are relevant for clinical practice (Brown et al 2001). What follows is based on current consensus.

Pre-eclampsia:

Pre-eclampsia is part of a spectrum of conditions known as the hypertensive disorders of pregnancy. Hypertension in pregnancy is usually defined as a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on two occasions (ideally at least four hours apart). Pre-eclampsia is defined as hypertension and proteinurea detected for the first time in the second half of pregnancy (after 20 weeks gestation) (Meher et al 2005).

Severe pre-eclampsia:

There is no widely accepted definition of pre-eclampsia. Nevertheless, the following are generally regarded as features of severe pre-eclampsia: systolic blood pressure of at least 160 mm Hg or 110 mm Hg diastolic, proteinurea (≥0.3 g/24h), reduced urinary volume (<400 ml to 500 ml in 24 hours), neurological disturbances such as headache, visual disturbances, and exaggerated tendon reflexes, upper abdominal pain, pulmonary oedema (fluid in the lungs), impaired liver function tests, high serum creatinine, low platelets, intrauterine growth restriction or reduced liquor volume (ACOG 1996, Brown et al 2000, Brown et al 2001, Meyer et al 2005).

1.4.3 Symptoms and signs

A frequent characteristic of mild pre-eclampsia is that women feel relatively well and generally have no symptoms. Women with severe pre-eclampsia, however, may feel unwell with symptoms such as headache, visual disturbances, epigastric or right upper quadrant pain, nausea, and vomiting or rapidly progressing oedema. Signs of pre-eclampsia include epigastric or right upper quadrant tenderness, intrauterine growth restriction / death and placental abruption (Nelson-Piercy 2006:6). Because of the multi-organ nature of pre-eclampsia, the presenting signs and symptoms can vary enormously; some women follow a slow and steady progress from mild through moderate to severe disease, others reaching catastrophic proportions within a very short time frame (Redman and Walker 1992:5).

1.4.4 Complications

Although outcome is generally good, pre-eclampsia is a major cause of morbidity and mortality for the woman and her child. It is a multi-system disorder with unpredictable, variable and widespread manifestations (Nelson-Piercy 2006:16). Pre-eclampsia accounts for an estimated one fifth of antenatal admissions (Rosenberg and Twaddle 1990), two thirds of referrals to day care assessment units (Anthony 1992) in the UK, and a quarter of obstetric admissions to intensive care units in France (Bouvier-Colle et al 1996). In 2003-2005 18 women died from eclampsia or pre-eclampsia in the UK (CEMACH 2007). Causes of severe maternal morbidity and mortality

from eclampsia were surveyed through UKOSS (United Kingdom Obstetric Surveillance System) from February 2005 to February 2006 (Knight 2007). Over thirteen months of the study, 209 confirmed cases of eclampsia were reported. This represented an estimated incidence of 2.7 cases per 10,000 births with a 95% confidence interval from 2.4 to 3.1.

There is a growing awareness of the high level of health problems women experience, even after an uncomplicated pregnancy and childbirth. Around 14% of women report health problems such as back pain, exhaustion, anaemia, haemorrhoids, headaches and emotional difficulties in the first eight weeks after the birth; and such problems continue for 10% in the subsequent 12-18 months (Glazner et al 1995). For women with pre-eclampsia, who are more likely to have had complications such as caesarean section or preterm birth, long term morbidity is probably higher (Brown et al 2000). In the Magpie Trial follow up study, only one third of women did not report any health problems, and even this may represent under-reporting (Magpie Trial Follow Up Study Collaborative Group 2007b). Women in the UK reported similar levels of health problems to women in other countries who participated in the Magpie Trial. However, mental health problems were reported by a quarter of women in the UK follow up, compared to just 6% of women overall in the Magpie Trial follow up (Magpie Trial Follow up Study Collaborative Group 2007b). This difference probably reflects substantial under-ascertainment in low and middle-income countries. The UK data are based on self-reporting and information from general practitioners; the true level of mental health morbidity may be even higher.

Pre-eclampsia can lead to problems in the liver, kidneys, brain, and to abnormalities in the clotting system (Meyer et al 2005). A range of life-threatening complications includes eclampsia, HELLP syndrome (**H**aemolysis, **E**levated **L**iver enzymes and **L**ow **P**latelets), disseminated intravascular coagulation (a combined liver and blood clotting disorder); and cardiovascular disease later in life. The commonest causes of death in pre-eclampsia are stroke and adult respiratory distress syndrome. Perinatal mortality is also increased with pre-eclampsia (CEMACH 2007).

There is also growing evidence that women who have had gestational hypertension or pre-eclampsia may be at increased risk later in life of hypertension, stroke, and ischaemic heart disease (Hannaford 1996:647, Wilson et al 2003, Bellamy et al 2007). For many women, developing pre-eclampsia can be a difficult and unexpected experience, especially if they become extremely ill, give birth too early, or if their baby dies. Psychological morbidity following a difficult pregnancy or labour, or perinatal death is well documented (Hughes 1998:145, Lyons 1998:123), although there are few data specific to pre-eclampsia (Meyer et al 2005).

1.4.5 Risk to the baby

The placenta is involved in pre-eclampsia, and so risks for the baby are increased. The placental manifestations lead to poor growth, placental abruption (premature separation of the placenta), and in severe cases, intrauterine death (Nelson-Piercy 2006:8). Pre-eclampsia is a major cause of perinatal mortality, contributing to 59 deaths per 10,000 births in the UK (Knight 2007). As delivery is the only cure, the hypertensive diseases become the commonest causes of iatrogenic prematurity (Hewitt and Newnham 1988, Shennan 2004:179). Such babies are at an increased risk of developmental delay and chronic ill health in childhood (Taylor 2000:345, Meyer et al 2005).

1.4.6 Aetiology

The underlying causes of pre-eclampsia and eclampsia remain unknown. Factors that appear to have a role include the placenta, maternal immune response, genetic predisposition, maternal disease, and diet. Whether an individual woman will develop this syndrome probably depends on which of these factors she has, and how they interact (Meyer et al 2005).

Placenta:

Pre-eclampsia is fundamentally a placental disorder. A common feature of pre-eclampsia can be uteroplacental ischaemia, and can be due to poor implantation or an excessively large placenta, for example in pregnancies complicated by diabetes, a multiple pregnancy (Nelson-Piercy 2006:8), or a

hydropic fetus (Vatish et al 2004). Pre-eclampsia can occur in pregnancies without a fetus (molar pregnancies) and in abdominal pregnancies, suggesting the placenta is of paramount importance (Campbell and Lees 2000:160).

Maternal immune response:

An immunological element to the disease process is evidenced by the effect of exposure to the paternal antigen (Shennan 2004:180). Normal pregnancy requires adaptation of the maternal immune response, so that the fetus, who also carries the father's genes, is not rejected as foreign tissue (Meyer et al 2005). Pre-eclampsia occurs more commonly in first pregnancies; in subsequent pregnancies with the same partner the immune intolerance is more complete, and the risk of pre-eclampsia is therefore lower (Meyer et al 2005). Miscarriages or terminations of pregnancy provide some reduction in risk in subsequent pregnancies (Shennan 2004:185).

Genetic predisposition:

Although the inheritance of pre-eclampsia has yet to be characterised, there is a strong familiar predisposition: a family history in either mother or sister increases the risk of pre-eclampsia four-eight fold (Shennan 2004:181). A number of genes are currently under evaluation for possible links with pre-eclampsia (Pridjian and Pushett 2002, Stanczuk et al 2007, Nishizawa et al 2008).

Maternal disease:

Underlying medical disorders, particularly those involving vascular disease increase the risk of pre-eclampsia. Thrombophilia is associated with severe early onset of pre-eclampsia (Dekker et al 1995). This is a group of conditions with a tendency for thrombosis, or blood clotting. They include disorders such as protein S deficiency, activated protein C resistance, Factor V Leiden mutation and autoimmune diseases such as antiphospholipid syndrome and systemic lupus erythematosus (Meyer et al 2005). Pre-existing diabetes and a pre-pregnancy body mass index (BMI) of ≥35 almost quadruple the risk: pre-existing hypertension, a booking diastolic blood

pressure ≥80 mm Hg and renal disease increase the risk, but it is not clear by how much (Duckitt and Harrington 2005).

Diet:

Nutritional factors have been suggested to be linked to the risk of pre-eclampsia. These include high calcium intake, oily fish, magnesium, zinc, selenium, vitamins C and E, folic acid, garlic and rhubarb (Meher et al 2005).

1.4.7 Identifying women at risk of pre-eclampsia

Women with pre-eclampsia are usually asymptomatic when the disease is first manifest therefore much antenatal care (measuring the blood pressure and checking the urine for protein) is directed at screening for this condition. There is no diagnostic test for pre-eclampsia, but there are risk factors with a particularly high association with pre-eclampsia. These include: maternal diabetes (Conde-Agudelo and Belizan 2000, Lee et al 2000), pre-existing hypertension (Caritis et al 1998, Conde-Agudelo and Belizan 2000), and renal disease (Cunningham et al 1990). Thrombophilia and autoimmune disease have a strong association with severe early onset pre-eclampsia (Pattison et al 1993, Stamilio et al 2000). Obstetric factors associated with high risk are multiple pregnancy (Long and Oats 1987, Coonrod et al 1995), history of pre-eclampsia in a previous pregnancy especially if severe or early onset (Sibai et al 1991, Caritis et al 1998, Hnat et al 2002), and a current hydropic (Scott 1958), or molar pregnancy (Taylor 1988:223). Other factors linked with pre-eclampsia, but associated with lower risk include first pregnancies (Taylor 1988, Coonrod et al 1995, Brown et al 2001), age less than 20 or more than 35 years (Ness and Roberts 1999, Conde-Agudelo and Belizan 2000), a family history of pre-eclampsia (Arngrimsson et al 1990, Cincotta and Brenneck 1998), and raised body mass index (BMI) (Sebire et al 2001, van Hoorn et al 2002), although more recently BMI has been questioned (Cnossen et al 2007).

1.4.8 Predicting pre-eclampsia

Despite continued research (Hofmeyr et al 2006, Brown et al 2007, Stanczuk et al 2007), there is still no test or tool to aid the early diagnosis of pre-

eclampsia or identify women at risk of developing eclampsia. Raised blood pressure and proteinuria are signs of this condition. Because, however, these are largely 'silent' to the woman, most women experience no symptoms of the illness and can become acutely ill without much warning in what appears to be a very short period of time. Based on recent UK estimations of eclampsia; most women who present with eclampsia will not have had a recent blood pressure or urine analysis test that was sufficiently abnormal to have identified them as at risk (Knight 2007). Blood pressure and proteinuria cannot be relied upon alone. Severe pre-eclampsia can develop within days of entirely normal observations in the antenatal clinic making the prediction difficult (CEMACH 2007). Consequently, pregnant women continue to present with severe pre-eclampsia that requires urgent and effective management. Although pre-eclampsia is the most common medical complication of pregnancy and is a dangerous condition, its complexity makes it poorly understood by doctors and midwives. Women are often unaware of both the condition and that they might be at risk of developing it.

Whatever the physical seriousness of the condition for the woman it is one that creates considerable psychological stress and anxiety about her own health and that of her unborn child. It remains unclear to what extent stressful experiences such as these impact on long-term psychological morbidity of women. Data from one study (Engelhard et al 2002) suggest that pre-eclampsia may predispose to posttraumatic stress disorder (PTSD). The data from this study recognise that PTSD may result from exposure to extreme psychological stress; stressful conditions being typically unpredictable and uncontrollable. It follows then that pre-eclampsia should be considered a condition with a potentially strong psychological impact and that the women recruited to the Magpie Trial were at risk of long-term psychological morbidity (Smyth et al 2008).

The following two sections describe the Magpie Trial and its follow up study. Much of the text has been taken directly from the trial protocols (Magpie Trial Protocol 1998, Magpie Trial Follow Up Study Protocol 2004) and the ensuing results papers (Magpie Trial Collaborative Group 2002, Magpie Trial Follow

Up Study Collaborative Group 2007a), Magpie Trial Follow Up Study Collaborative Group (2007b).

1.5 Why the Magpie Trial was needed

In 1995, magnesium sulphate was shown to be the anticonvulsant of choice for women with eclampsia (The Eclampsia Trial Collaborative Group 1995). The trial included 1680 eclamptic women, and produced compelling support for the use of magnesium sulphate. Women had a 52% lower risk of recurrent fits after treatment for a first fit with magnesium sulphate compared to diazepam or phenytoin. They were also less likely to die after being treated with magnesium sulphate than with diazepam or phenytoin (although these changes in death rates were not statistically significant). No clear evidence emerged that treating women with magnesium sulphate was either advantageous or disadvantageous to the fetuses, at least not in the short term. These results had major impact on both practice and policy throughout the world. As a result magnesium sulphate for the treatment of eclampsia was included in the essential drugs list of the World Health Organisation (WHO 1997) and recommended in the practice guidelines produced by the Royal College of Obstetricians and Gynaecologists, London (RCOG 1999).

Having switched to magnesium sulphate for women with eclampsia, many clinicians were also reviewing their policies for anticonvulsant prophylaxis. Consequently some obstetricians began using magnesium sulphate for women with pre-eclampsia, leading a number to propose that all women with pre-eclampsia should receive it (Anthony and Rush 1998, Graham 1998, Khan et al 1998). However, others remained in equipoise and challenged widespread prophylactic use in pre-eclampsia (Thornton 2000), considering that at this time there was a window of opportunity to properly evaluate the use of magnesium sulphate for women with pre-eclampsia (Rubin 1998). A survey of obstetricians in the UK and Republic of Ireland around the same time confirmed that many would consider collaborating in a controlled trial of magnesium sulphate versus placebo in women with pre-eclampsia, providing further justification for the need for the Magpie Trial (Gülmezoglu and Duley 1998).

1.6 The Magpie Trial (MAGnesium sulphate for Prevention of Eclampsia)

The Magpie Trial was a large international randomised placebo controlled trial designed to evaluate the effects of magnesium sulphate on women and their babies. It was funded by The Medical Research Council (UK) [ISRCTN86938761]. The aim was to find out if, overall, women with pre-eclampsia or their children, or both, did better when given magnesium sulphate rather than placebo, regardless of whether treatment was started before or after delivery and irrespective of any previous anticonvulsant therapy. Women were eligible for trial entry if they had pre-eclampsia and there was clinical uncertainty about whether to use magnesium sulphate. Women were included irrespective of whether they had given birth (24 hours or less postpartum) or their pregnancy was singleton or multiple. Most women were recruited whilst on the labour ward. The decision to offer participation was usually made by the obstetrician; either an obstetrician or a midwife could enrol women.

A detailed description of the Magpie Trial and its results is provided in the main results paper published in The Lancet in 2002 (Magpie Trial Collaborative Group (2002) Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. The Lancet; 359: 1877-90, see Appendix 1). For purpose of context, Magpie was conducted in 33 countries and involved 10,141 women. A follow up study was conducted in 19 countries, involving 4782 women. Hereafter information presented within this thesis relating to the Magpie Trial and its follow up study will only relate to the UK component.

1.7 The Magpie Trial Follow up study

The main objective of the follow up study was to assess whether *in utero* exposure to magnesium sulphate has any clinically important effects on the child's chance of surviving without major neurosensory disability. The specific research questions were whether, for the offspring of affected mothers exposure to magnesium sulphate affects: the risk of the child dying, the risk of severe cerebral palsy, the risk of blindness or deafness or the risk of

developmental delay. For the woman whether it affects her longer-term risk of death or serious morbidity.

1.7.1 Methods

Children born to women randomised to the Magpie Trial were part of the follow up study (n=841). Ascertainment of deaths after discharge from hospital was through the Office of National Statistics. The families' current address was obtained from a range of sources, including trial data collected at discharge from hospital, the Office for National Statistics, and the National Health Service Tracing Scheme. Families were contacted if there was at least one surviving child. If the mother had died, the child's carer was contacted. Between July 1998 and November 2001, 804 women were recruited to the Magpie Trial at 67 UK hospitals. Follow up was from October 2002 until May 2004. Thirty women were excluded from tracing leaving 774 eligible for follow up (Figure 1.1).

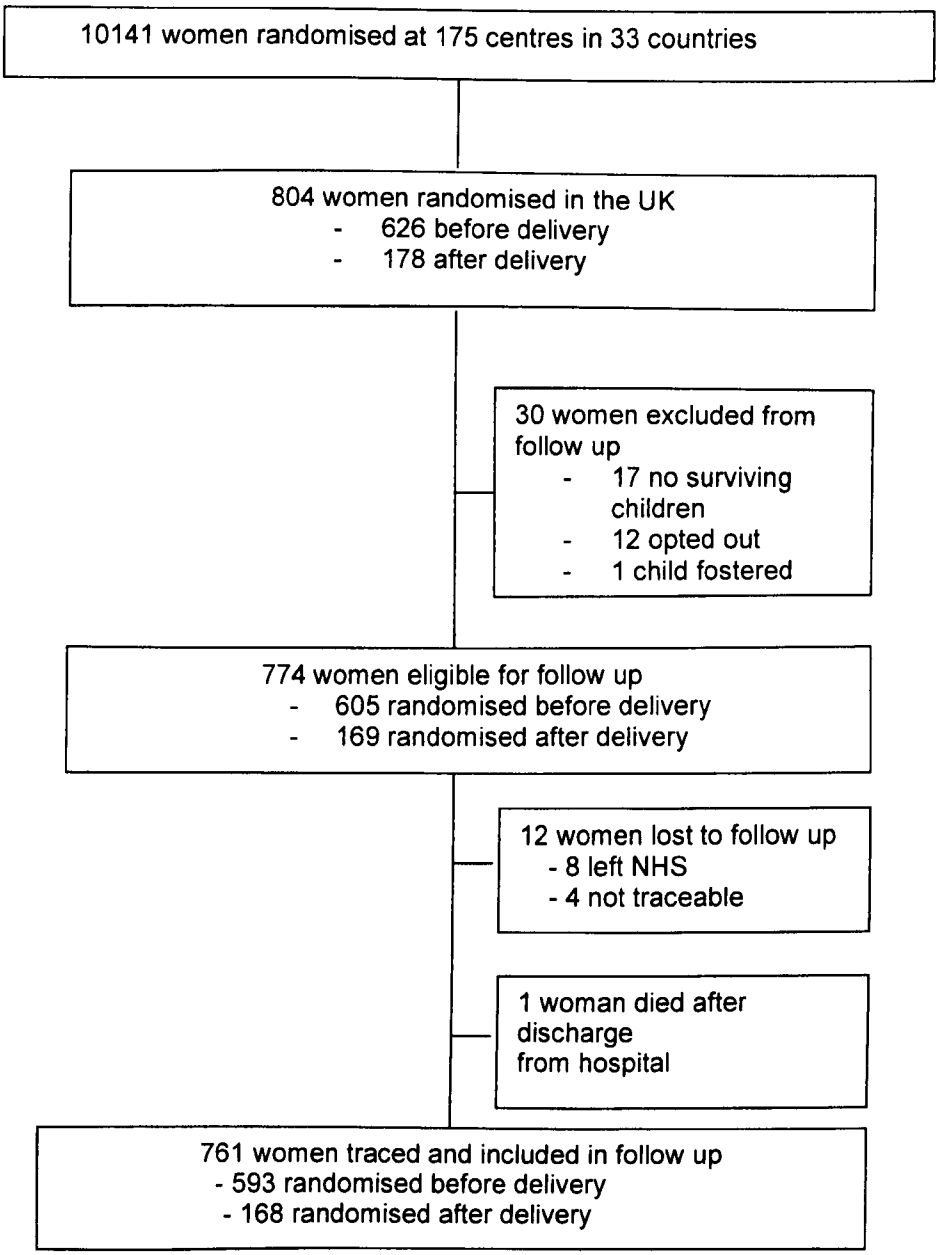


Figure 1.1 Consort flow diagram for women recruited in the UK and followed up

The clinical co-ordinator (LD) and I wrote to identified families describing the follow up study, enclosing a change of address card so they could let us know if they moved, and giving them an opportunity to 'opt out' from participating in it (Appendix 2). This letter was sent with a birthday card for the child's first birthday (Appendix 3). For some children the follow up study started after their first birthday and a greeting card was sent instead. After receiving the information about the follow up study some women telephoned,

either to find out more about pre-eclampsia, or about the Magpie Trial and its follow up. This gave them the opportunity to talk about their experiences of pre-eclampsia and joining the trial. It was apparent from these conversations that although recruitment to the trial was some time ago, their memories of the experience were still very detailed.

The women's general practitioner was sent a questionnaire when the child was 18 months old. If the woman and child had different general practitioners, both were contacted. The general practitioner questionnaire included questions about the child's general health since birth, recent consultations (excluding routine assessments and immunisations), neurosensory function, any diagnosis, prescribed medication, and admission to hospital. A separate section asked about the mothers' health, possible long-term sequelae of pre-eclampsia, prescribed medication, and admission to hospital. Those general practitioners who did not respond were sent reminders, or contacted by telephone.

When the child was around two years old, a questionnaire pack was posted to the family. The questionnaire relating to the child incorporated the Ages and Stages Questionnaire (ASQ) (Squires et al 1999) (Appendix 4). Parents or carers, with or without help from a health worker, could complete the postal questionnaires. The ASQ included 30 questions covering five domains: communication, gross motor, fine motor, problem solving and personal-social. Responses are 'yes', 'sometimes' and 'not yet'. These are scored and sub-totalled by domain. To be classified as having no developmental delay, the child has to score at least adequately in all five domains. Questionnaires are relevant for children aged 4 months to 5 years. Up to 24 months, age is adjusted for gestation at birth. Each questionnaire is valid for four weeks either side of the target age. Another section of the ASQ addresses general parental concerns and was not scored. Two questions were added about use of health service resources.

Enclosed with the child's questionnaire was a questionnaire asking women about their own health (Appendix 5). Some questions related to the woman's

fertility, and how this had been influenced by her experience of pre-eclampsia. It also asked three simple questions about her experience of participating in the Magpie Trial. Responses to these three questions form part of the analysis presented in this thesis, and are reported in detail in Chapter 4.

Children who scored adequately on the ASQ for their own age, or for an older age group, were considered screen negative, and therefore not needing further evaluation as it was unlikely that they had any developmental delay. Children who did not score adequately on the ASQ (regardless of whether it was completed within the correct time frame) were considered to be screen positive and as possibly having some form of developmental delay. Also considered screen positive were children with a problem reported in the general questions, (which covered any parental concerns relating to walking, talking, hearing, understanding and vision), any whose ASQ was incomplete and could not be scored, and those who scored adequately on the ASQ for children in a younger age group. All screen positive children and a sample of screen negative children were invited for a clinical and neurodevelopmental assessment using the Bayley Scales of Infant Development (BSID-II) (Bayley 1993).

I was responsible for contacting families by telephone to offer a home visit, for further assessment. Most families, although often surprised that a member of the study team contacted them, were receptive to the idea of a home visit. The aim of the home visit was to confirm whether or not the child had neurodevelopmental delay, or any other significant problem; and if so, to collect information that would, if possible, establish a diagnosis. Parents were asked about their child's current health and development, and the child was tested using the Bayley Scales of infant Development (BSID-II) (Bayley 1993). The visits were conducted by myself or a psychologist, both trained in the use of the BSID-II. We met every three months and conducted some joint visits.

Overall, 140 children whose mothers were randomised *in utero* were considered screen positive, of whom 108 had a home visit. One hundred and twenty four 'screen negative' children were also offered a home visit, and 94 were performed. At the time of the home visits most children were between 25-36 months old. A full description of characteristics of women included in the follow up study is provided in Chapter 3. All assessments of children and their mothers were made blind to treatment group. If women asked about their allocation, this information was sent once data collection was complete.

When a home visit was conducted, the opportunity was taken to measure the woman's blood pressure and to ask her about possible hypertension and problems or concerns with her own health. Home visits lasted approximately two – three hours.

During the time the follow up study was in progress the main Magpie Trial results were published (Magpie Trial Collaborative Group 2002) (Appendix 1), and soon after a lay summary was posted to all women (Appendix 6).

1.8 Description of women recruited to the Magpie Trial in the UK

The following section provides a brief summary of the characteristics and circumstances of the women recruited to the Magpie Trial. This is given in order to contextualise the literature review (Chapter 2) and convey how published empirical qualitative work has been concerned little with the unique experiences of those recruited to perinatal trials whilst experiencing a life threatening illness.

The women were recruited at a time when they were likely to be having intensive monitoring, and there was often a concern about the health of the baby as well as of the women themselves. Care would usually consist of bed rest, restriction of oral fluids, close clinical monitoring (blood pressure checked every 15-30 minutes, tendon reflexes checked hourly, and the urine measured hourly), insertion of urinary catheter and intravenous infusion and, sometimes, the baby being delivered early. Care that was attributed solely to the Magpie Trial was an extra intravenous line and frequent unobtrusive

observation of the respiratory rate. Clinicians also made the decision to deliver women within 24 hours of recruitment to Magpie.

Of women recruited to the Magpie Trial in the UK (n=804), most (78%) were pregnant at the time, just under half (44%) had their labours induced, and nearly half (47%) were delivered by caesarean section. The decision to deliver women within 24 hours of recruitment to Magpie was often made by the recruiting clinician. As a consequence over a quarter (29%) of women delivered their babies preterm (less than 34 weeks gestation), often resulting in increased mortality and morbidity.

Although many women entering the Magpie Trial were not in acute emergency situations, many were experiencing a dangerous and frightening condition; just under half (46%) had severe pre-eclampsia and a quarter (27%) imminent eclampsia. Since severe pre-eclampsia can be life threatening for both the woman and her unborn child, most women (85%) taking part in the Magpie Trial were cared for on an obstetric high dependency unit (HDU). As a third of eclamptic fits occur postpartum, intensive monitoring was often continued for 48 hours after delivery.

For many women developing pre-eclampsia is an unexpected and very difficult experience. Women offered randomisation to the Magpie Trial were extremely ill and many had very little warning of the disease developing. Due to this unpredictability and the speed at which it can develop, many women may have had little understanding of the disease before it became evident, causing further anxiety.

1.9 Outline of the thesis

The thesis consists of 9 chapters. This opening chapter has provided an introduction to the QUOTE Study and the context in which I undertook the study. The background to the QUOTE Study is then provided. It begins with a comprehensive overview of pre-eclampsia (and eclampsia); which is the most common medical complication of pregnancy. These are presented in order to put in to context the situation the women were in when they were

asked to consider taking part in the Magpie Trial, as most were experiencing a severe form of pre-eclampsia. The chapter also provides an overview of the Magpie Trial and its follow up study. Chapter 2 provides a critical review of the literature pertaining to the wider context of participation in clinical trials in health care. The chapter begins with focusing on the experiences of pregnant women in trials. Because of the paucity of available evidence exploring the experiences of women recruited to clinical trials during pregnancy, particularly those having experienced a pregnancy-related emergency, other related clinical trial situations in health care are explored and offer useful illustrations as a way of understanding and learning about trial experience.

The study design and rationale for the selection of a multi-method approach and theoretical basis are presented in Chapter 3. As described the study was carried out in two distinct parts: questionnaires and interviews. A description of study procedures, selection of participants and data analyses at each point are provided. Chapters 4 - 8 present the results from the study. Chapter 4 pertains to the data obtained from the postal questionnaires; Chapter 5 contains the results from the semi-structured interviews. A description of the sample, the response rate and characteristics of the women are also presented. Chapters 6 - 8 provide a detailed description of the results. The final chapter, Chapter 9 presents a discussion and summary of the study results. Focus is placed on the issues taken into account by the women when considering joining the Magpie Trial. The background influences and the impact pre-eclampsia had on their decision-making experience are also given attention. The methodological limitations of the study and the consequences these may have had on the study findings are also considered. Further consideration is given to the implications of my findings for future research and practice.

Chapter 2

Literature review of participants' views of taking part in trials

2.1 Introduction

In modern healthcare there is greater democracy, with public and patient involvement in health care being actively encouraged (Best Research for Best Health 2008). One aspect of this is the involvement of users in the conduct of health care research. There is drive for promoting the hands-on involvement of users in all aspects of design and conduct of research (Hanley et al 2001, Hanley et al 2003, Oliver et al 2004, NICE 2006, WHO 2006, MRC 2007, NRES 2008) also coming from users themselves (AIMS/NCT/MA 1997, Goodacre and Lockwood 1999, Thornton 2006, Thornton 2008, Cochrane Consumer Network 2008). Groups such as INVOLVE (2008) are committed to promoting public interest in NHS, public health and social care research. Involvement includes, for example, the public advising on which research should be performed, as well as assisting in the design and running of projects. Another group, the James Lind Alliance (2007) acknowledges the importance of user involvement and partnership in the identification and design of research. The remit of the James Lind Alliance is to help researchers and clinicians identify areas in need of research relevant to users and promote researchers to ask the right questions in the right way, so ensuring research therefore is relevant to users by promoting their involvement in the process. These groups emphasise the significance of user involvement and partnership in the identification and design of research. Exploring the views of trial participants is one part of this spectrum of activity and the value of understanding the experience of taking part in trials from the perspectives of those involved is now recognised.

Prompted by these proposals (and others before) a growing body of research has begun to study participants' or potential participants' views of health care research, including randomised trials. There is a wealth of literature exploring the many components of participant involvement, and which can be considered under a number of broad categories. Most studies to date have

concentrated on the ethical issues of performing research trials in clinical practice (Howard-Jones 1982, Herxheimer 1988, Verdu-Pascual and Castello-Ponce 2001, Knudson 2001, Brody et al 2005), and whether research participants are fully informed (Hewlett 1996, Joffe et al 2001, Iltis 2006) and therefore adequately consented before agreeing to take part in trials (Hansson 1998, Ferguson 2001, Stevens and Pletsch 2002). The double standards regarding consent for research and consent for clinical care have also been debated (Chalmers and Silverman 1987, Oxman et al 2001, Mazur 2003, Worthington 2004). Others have explored reasons for participating in (Pickersgill et al 1998, Ellis et al 2001, Madsen et al 2002, Eng et al 2005) and declining participation (Verheggen et al 1998, Jenkins and Fallowfield 2000, Salomons et al 2002, Snowdon et al 2005, Snowdon et al 2007); as well as barriers to participation (Fallowfield et al 1997, Langley et al 2000, Grunfeld et al 2002, Sharp et al 2006). The possible interventions that can be used to improve recruitment to research have also been explored (Albrecht et al 1999; Donovan et al 2002, Cambron et al 2004). In-depth qualitative interviews have been conducted in order to appreciate participants' understanding of trial design (Snowdon et al 1997, Fallowfield et al 1998, Featherstone and Donovan 2002, Robinson et al 2004, Canvin and Jacoby 2006), as well as informing participants about study results (Partridge and Winer 2002, TACT 2006, MacNeil and Fernandez 2006, Avins et al 2008) and their response to receiving them (Garcia 1987, Snowdon et al 1998a, Kenyon et al 2006, Shalowitz and Miller 2006).

This chapter presents an overview of this literature in order to explore the issues that I perceived as salient to the QUOTE Study. There is a wealth of literature published about the views of participants in randomised trials. Little, however, explores the unique experiences of those being recruited whilst pregnant and even less explores the perspectives of those recruited around the time of delivery, whilst experiencing a pregnancy related illness. In order to identify systematically and present a representative body of literature that relates to women's experiences of joining perinatal research two separate literature searches were conducted with the support of two independent

information retrieval specialists (LH, AB). No restriction was placed on type or country of publication.

2.2 Search strategy

The research questions addressed were as follows: to assess the experiences of pregnant women being recruited to randomised trials; to provide a critical overview of the issues as identified by the women themselves. Both information specialists used the same electronic bibliographic database to search: Medline (1966 to June week 2 2006), AB also searched CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1982 to June week 2 2006). Both were provided with a thorough description of the study prior to searching; however both identified different medical subject headings (MeSH) in order to do the searching. Identifying publications involved a variety of other techniques carried out solely by myself. For example, citation tracking was used (following up reference lists in the bibliographies of papers and reports). Work citing authors known to be active in the field was also followed-up. Contacts with experts were made to identify other potentially relevant published or unpublished studies. Handsearching of journals and texts were also performed and the websites of the Department of Health, Cochrane Qualitative Research Methods Group and the NHS Health Technology Assessment Programme were utilised.

Several difficulties in electronic searching of the literature were encountered, even with the combination of literature searching expertise and my own subject knowledge. Most difficulties related to developing a strategy that would identify *qualitative* studies that have explored participants' views of *quantitative* methodologies. It became apparent there was varied and imprecise use of the term *qualitative*. This was emphasised by the wide range of study designs and collection methods cited in the publications. Searches for qualitative studies triangulated with quantitative methodologies exploring the research area can identify a number of potentially relevant records. The first search retrieved an unmanageable number of potentially eligible records (n=6185). Viewing their titles identified that the vast majority were false positives, e.g. papers that had little to do with pregnant women

and trial participation. This first search made retrieval to eliminate or include reports on an individual basis logistically impossible. The second search resulted in a more targeted and precise retrieval of literature (n=177). The third search using CINAHL identified 3,348 reports. It was evident that after performing the added searches (those carried out solely by myself) much of the relevant literature was not identified. The additional searching therefore proved to be extremely worthwhile in identifying additional empirical studies. The electronic bibliographic database search strategies are fully described in Appendix 7.

The literature presented within this chapter will initially centre on the specific experiences of those recruited to studies in pregnancy. Research to date in this area has predominately focused on the experiences of those recruited to trials whilst in early pregnancy rather than around the time of delivery. These situations are not directly applicable to women recruited to the Magpie Trial, as those joining Magpie were recruited close to the time of delivery. The research does though provide a valuable insight into understanding pregnant women's experiences of joining research. Because of the paucity of pregnancy-related literature, the wider issues of trial involvement, drawing on research from other areas of health care, have also been examined. There is a wealth of publications exploring the views of those involved in many aspects of health care research. It was considered worthwhile to draw upon this literature in order to provide additional insight into the complex components of trial participation. Limiting the review to the perinatal experience would have omitted some of the important literature that has, in part, influenced this study. However, caution should be exercised when drawing conclusions from comparing trial experiences between different disciplines of health care. Conclusions may not always be easily transferable. Reviewing this literature does, however, provided useful insights into the broader, more general aspects of trial involvement.

2.3 Exploring participants' views of randomised trials in the perinatal period

Although trial investigators and clinical staff have undoubtedly acquired much anecdotal information about participants' views of their trial experience, few empirical studies have been carried out that explore participants' views and experiences of joining trials relating to the perinatal period. Only ten published empirical studies (13 reports) were identified in the literature search that have formally investigated pregnant women's views of trial participation and therefore relate very closely to this present study. Much of this work has explored the decision-making processes of pregnant women being asked to participate in trials, and has identified factors affecting their willingness to agree (East and Colditz 1996 & East et al 2006) or decline participation (Mohanna and Tunna 1999, Dorantes et al 2000, Baker et al 2005). Other studies have focused on participants' understanding of trial information (Ferguson 2000, Kenyon and Dixon Woods 2004, Kenyon et al 2006 and Dixon-Woods et al 2006), or views about being involved generally in research (Elbourne 1987). In some studies women were asked to hypothesise about unreal situations (Weston et al 1997, Rodger et al 2003, McLeod et al 2004). Little of the reported work however, was conducted with women experiencing a pregnancy related illness, and so it has only indirect relevance to the women participating in the Magpie Trial. Additionally much of the data were derived from postal surveys alone (7 studies), therefore lacking the richness of information that can be gained from in-depth interviews.

These ten empirical studies have been explored and key areas identified that have particular relevance to the QUOTE Study (see Table 2.1 for summaries, pages 42, 43, 44). The first of these areas was an examination of the potential benefits of providing information to women about trials in the antenatal period.

2.3.1 Benefits of providing information about perinatal trials in the antenatal period have not been confirmed

It is currently recommended that women should not be asked to consent to take part in perinatal research unless they have been given written information about it earlier in the course of their pregnancy (AIMS/NCT/MA 1997). User groups have recommended whenever possible information about trials should be given in early pregnancy and a period of time allowed for discussing the trial; consent could then be given at a later stage. In response to this suggestion, those involved in perinatal trials more recently have provided study information to be given to women in the antenatal period (see, for example, the Oracle, Magpie and Release Trials).

However, the benefits of providing perinatal trial information early in pregnancy are not clear nor have they been adequately evaluated or confirmed. Those that have explored this issue with trial participants have done so only at a relatively superficial level, as the focus of their research was on reasons for withholding consent (Mohanna and Tunna 1999) or general attitudes to the trial (Ferguson 2000, East and Colditz 1996, East et al 2006). Nonetheless, their conclusions cast doubt on the claim that informing women early in their pregnancy about perinatal trials leads to greater understanding and satisfaction with the information they receive or with their trial experience overall.

The study by Mohanna and Tunna (1999) concluded that informing pregnant women early in their pregnancy about a trial they might become eligible for has different implications for different women. Many of those interviewed could not see the relevance of the research to their situation; and even women who were identified as at high risk of becoming eligible, stated they would decline participation as the trial was not relevant to them. This study highlighted the difficulties some women can have envisaging their situation if a potential risk is realised; and how they will respond to that situation. Providing trial information prior to a clinical event or talking to women about the likelihood of them becoming eligible for enrolment may not therefore be valuable for all women.

The time lapse between information provision and actually becoming eligible can also be problematic, as during the intervening period many women may forget being told about the trial specifics or even about the trial itself. One study by East and colleagues (2006) found that some women expressed a preference for study information earlier in their pregnancy, even though study brochures had been widely distributed at parenting classes and antenatal visits. This indicated that women either did not recall receiving this information during their pregnancy or in fact did not receive it. Similarly Ferguson (2000) found that a high proportion (88%) of women could not recall being told about a perinatal trial in the antenatal period, several being adamant that this had not occurred, although the trial protocol specified that one of the researchers would attend antenatal classes in order to inform women and midwives about it. Informing women about possible perinatal trials antenatally is not therefore without its difficulties. Indeed, these studies suggest that attempts to inform women in advance, for whatever reason, are largely unsuccessful.

There are other potential difficulties with routinely presenting women with research information antenatally. For many the risk of experiencing adverse events in their pregnancy is small and to present all women with a detailed discussion of each potential complication of pregnancy and then the accompanying trial information, can further increase the 'medicalisation' of childbirth and unnecessarily detract from it being a normal event. Informing women early in their pregnancy may in fact cause needless anxiety for them, especially when there is so much information pregnant women need to know and understand during the antenatal period. A study by Baker et al (2005) identified that women do recognise the difficulties clinicians face when conducting perinatal trials, and they appreciate that informing women who are not actually experiencing the particular clinical event is not always appropriate. The difficulty here, as occurred in the Magpie Trial, is predicting which women will have the adverse event. Giving information in advance to all does have the potential to cause unnecessary worry. Vernon and colleagues (2006) have questioned this way of telling women about research. They propose that informing women in the antenatal period can bring about a

conflict with promoting 'normality' in pregnancy and labour; and routinely presenting women with research information about possible complications and risks unnecessarily detracts from labour as a normal physiological process, as for many women the risk of experiencing these problems is small.

In conclusion there is little consensus regarding the most appropriate time in pregnancy to provide information about perinatal trials. There are perceived benefits (discussing the study with women at a time when they are less likely to be rushed and under stress); however, they are not clear and have yet to be confirmed.

2.3.2 Benefit to woman herself or baby are key motives to participating in perinatal research

Factors that influence women's decisions about whether to participate in research during their pregnancy have been explored by several researchers (Elbourne 1987, Mohanna and Tunna 1999, Dorantes et al 2000, Ferguson 2000, Rodger et al 2003, McLeod et al 2004, Baker et al 2005, Kenyon et al 2006). It is evident that pregnant women participate in research for many reasons, and there are many influences on the decision-making process. The design of the trial, the type and style of information available, the manner in which it is conveyed, and by whom, all appear to effect the likelihood of a woman agreeing to take part (Mohanna and Tunna 1999). Other influences include whether the participant understands the nature of the study (Dorantes et al 2000), as well as the process of recruitment and practical issues such as convenience (Baker et al 2005).

Principal motivators for trial participation, however, appear to be the perceived benefit to the women themselves and/or their baby and altruism – the belief that joining will help other women and their babies and medical research. With the exception of two studies identified in the literature (Elbourne 1987, McLeod et al 2004), women's desire and willingness to help other women is only expressed in the context of there also being some benefits to either themselves or their baby. Kenyon and colleagues (2006)

examined trial participants' interpretation of study information provided for a perinatal trial and concluded the main motivation for trial participation was the possibility of an improved outcome for the baby. The second and less prominent motivation was the opportunity to help others, but this was conditional on there being no personal risks to either themselves or the baby.

Other researchers report similar findings. Rodger and colleagues (2003) asked pregnant women whether they would be willing to participate in a hypothetical trial of heparin injections. Potential benefit to the health of the unborn child was ranked as the most important determinant of willingness to participate, followed by benefit to personal health, and altruism. Ferguson (2000) confirms this finding; a large proportion of women join perinatal trials in order to secure better treatment, help future women or to assist the doctor. Others have identified a perception of low risk to either the women themselves (Baker et al 2005) or the baby (Dorantes et al 2000) as primary motivators.

What is noteworthy is that those identifying altruism alone as a motivator for participation were involved in what could be considered low risk trials; one a hypothetical situation (McLeod et al 2004), the other assessing pregnant women's preferences about holding their own obstetric records throughout pregnancy (Elbourne 1987). The first of these studies (McLeod et al 2004) sought the views of pregnant women regarding their participation in a hypothetical trial comparing planned vaginal birth to planned caesarean section for twins. Of the sixty-four women recruited, altruism was the most common (90%) reason given by the women for agreement. Preference for a specific mode of delivery was the reason given by those declining participation by all women. Women participating in the hand-held records study (Elbourne 1987) discussed their wish to help others, both at the time of the study and in the future.

The issue of pregnant women withholding consent to trials has been explored (Mohanna and Tunna 1999). The purpose of the study was to explore why women chose *not* to participate in a preterm drug trial. The results indicated

that a protective duty to the unborn baby and the difficulty associated with balancing potential adverse events or side effects against the consequences of not taking part were influential.

These findings cumulatively indicate that the most important factors in a woman's decision to consent are related to her own situation. Ultimately, when women are asked to consider joining research trials it is the prospect of either protection or benefit to the woman herself or her baby more than the duty to be a 'good citizen' that influences their decision. Altruistic motives are just one of many factors that influence trial participation. Relatively few studies, however, have directly sought the views of women regarding this issue.

2.3.3 Double standards of consent to research and clinical practice

Recently there has been debate and controversy in the literature regarding the different standards of consent required for clinical procedures compared with what is required for clinical research. Mazur (2003) argues that the need for patients to fully understand is greater in clinical research because participation is voluntary, alternatives may exist, the participant may not benefit and could be harmed by participation. His position is supported by Worthington (2004) who makes a clear argument proposing the need for different criteria for consent in the trial setting, compared with what is required in clinical practice. He acknowledges exchange of information is crucial in both settings, albeit in different ways and, argues that while unknowns apply in any medical situation, the risk/benefit equation is different in the research setting, especially if the participant can derive little personal therapeutic benefit. In the research situation choices may well be governed by altruism or financial gain, rather than individual medical needs; there may also be less empirical data available to offer the volunteer, in order to inform or reassure him/her about likely outcomes of a drug or medical procedure. Worthington concludes: consent issues are not the same in the two settings, even if the ethical principles are.

In contrast Thornton (2005:468) questions this divergence of requirement for consent to treatment and consent to research. A trial participant herself (breast ductal carcinoma in situ trial) she asks "Why should randomisation – often to treatments that are 'standard' – require especially onerous informed consent?" She advocates a much more flexible approach and recommends that trial participants and patients be given every opportunity for easy access to the fullest possible information. Others also raise questions regarding the double standards required for consent in clinical practice and that which is required for research (Chalmers 1986, Chalmers and Silverman 1987, Chalmers 2003). Anxiety remains about the process of informed consent for researchers; however, the level of information provided in a formal research setting is often much greater than ordinary clinical practice. In clinical practice patients may receive little or no information and no guarantee that their experience of treatment will be used scientifically to evaluate care for others in the future (Chalmers and Silverman 1987).

In ordinary clinical practice it is necessary that clinicians evaluate how to impart information, and to what extent they will make clear the consequences of treatment choices, especially if they are uncertain. Although in all disciplines of health care a truthful and open approach is desirable, one of the challenges is to be able to estimate how much information should be given and at what time. Provision of the right amount of information for a particular patient is an important part of clinical practice. Little distinction, however, is made in current literature or in published guidance between the requirements for consent in research and consent in ordinary clinical practice. A document that has recently come into effect provides doctors with guidance on decision-making in the context of treatments, and states the same guidance applies to include decisions in taking part in research (GMC 2008).

On an every-day basis clinicians provide patients with medical treatments, (many of which have never been scrutinised in a randomised trial), after providing very little background information about the intervention. It is not clear why an intervention already being used in routine health care requires

informed consent within the research setting. In ordinary clinical practice, well-intentioned practitioners may prescribe the same intervention in good faith. It is proposed that it seems illogical to require a higher level of consent to a treatment given in a trial than would be required in normal clinical practice (Chalmers and Lindley 2000:266, Chalmers 2003). In the words of the paediatrician Richard Smithells: "I need permission to give a drug to half my patients, but not to give it to them all" (Smithells 1975, cited by Chalmers 1986).

In the absence of evidence from randomised controlled trials, it has been suggested that clinical decisions are often made randomly and in a haphazard way (Chalmers and Silverman 1987). Why then is there so much concern when the randomness is formalised in a controlled way? Properly designed experiments are more effective than poorly controlled experiments in containing the risks posed to individuals by the unpredicted adverse effects of treatments (Chalmers and Silverman 1987). It cannot be assumed that trial participation places people at disadvantage compared with standard care. The contrast between the procedures required in research and everyday clinical practice is striking. The distinction and apparent double-standard between research and routine care places a greater responsibility on researchers than clinicians to satisfy the consent process. There are established ways of giving information to patients and of obtaining consent in normal clinical practice, and it has been argued that we should think carefully about changing these merely because a controlled trial is being carried out (Chalmers 2003). Trials cannot be considered unethical just because participants have suboptimal understanding (based on the researcher's denotation). Lindley (1998) argues that randomisation into a well conducted, randomised controlled trial may well be 'best practice' for many clinical situations, perhaps even 'better' practice than is given in clinical care. Double standards for the consent process promote informal therapeutic experiments on uninformed patients that comprise much of everyday clinical practice - the corollary being that these people are perceived to be in less need of protection than are the relatively small number who are involved in planned, properly controlled clinical research (Chalmers and Silverman 1987).

2.3.4 Participants' understanding of the purpose of trials is often incorrect; trial practices including placebo, randomisation & blinding are poorly understood

There has been much debate, much beyond the remit of pregnancy and childbirth, about the ethical problems associated with the quality of informed consent and how problematic that can be for both the researchers (Hansson 1998, Pullman and Wang 2001, Tattersall 2001, Cassell and Young 2002) and those participating (Snowdon et al 1997, Power 1998, Stuijvenberg et al 1998, Thornton 1998, Goodare and Lockwood 1999, Goodare 2002, Spencer and Dawson 2004, Goodare 2006). In conducting clinical trials, researchers must meet certain ethical standards, first established by Nuremberg Code on research ethics in 1947. The type and degree of information required as part of an informed consent process has more recently been set out by the World Medical Association's Declaration of Helsinki, which states that the potential participant must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, the affiliations of the researcher, anticipated benefits and potential risks of the study and the discomfort it may entail (WMA 2004).

An interesting finding in Ferguson's (2000) work relates to the responses from the participants when asked to compare information they received as a clinical trial participant with information they were given in clinical practice. In general, participants felt they received more information when participating in trials. Several were keen to emphasise that the greater amounts of information they received during the trial were no reflection on their caregivers' usual practice.

That consent is the key issue for both researchers and participants is not disputed, but how to resolve the problems around informed consent has received less attention and is less clear. Given the concerns about ensuring fully informed consent, is it surprising that participants' understanding of perinatal trials and the methods involved have received so little empirical attention. Some interest has begun to be shown in understanding how *informed* participants are about participating in clinical research. Participants

are now being asked whether they felt they had received enough information about the research study, how well they felt they understood this information, and whether they were given sufficient time and encouragement to ask questions (Ferguson 2000). There is evidence that participants do not always adequately understand the purpose of the trials they join. Understanding the purpose and the perceived importance of a study have been identified as significant factors influencing the decision to join (Dorantes et al 2000). In a review of the literature however only a few studies have focused on asking participants to assess the information they receive.

Two of these studies, which are perhaps most closely linked to the situation of those recruited to the Magpie Trial, are by Ferguson (2000) and Kenyon and Dixon-Woods (2004) and (2006). Both groups of researchers explored trial participants' understanding of the research as their primary focus, each having their distinct approach. Ferguson (2000) used structured interviews to explore participants' understanding of an intrapartum trial. The author did not attempt to determine how much each participant had in fact understood; rather the focus of the study was understanding of the trial from the point of view of the participant regardless of whether or not their recollections were 'accurate'. The issue under investigation was not: are clinical trial participants adequately informed, judged by some objective criterion; but rather, do participants themselves feel that they are adequately informed?

In comparing levels of satisfaction with trial information between women participating in a labour drug trial with those who took part in other medical research trials, Ferguson (2000) concluded that women in the labour trial were generally less satisfied than those in the other trials with the information they had been given. They reported lower levels of understanding of trial information (91% versus 100%), they asked fewer questions and were less satisfied with the answers given. Information that women would have found useful to know included more detail about the way the drug worked, possible side-effects, alternative treatment options and their potential side-effects.

Although Ferguson (2000) found that in general women felt they were given appropriate amounts of information, and reported a reasonable level of understanding of that information, this cannot be assumed to mean that participants are able to assimilate the information they are given. Participants' perception is one issue; the reality of the situation could be quite different. Participants may feel they have reasonable grasp of a concept, but if this were to be tested it might not, in fact, be correct.

Kenyon and Dixon-Woods used postal questionnaires (Kenyon and Dixon-Woods 2004) and interviews (Kenyon et al 2006), to focus on establishing whether participants' perceptions of the Oracle Trial were actually 'accurate'. The researchers evaluated participants' interpretation of trial information given to them. They used content analysis to analyse the text given in response to a question on a postal questionnaire asking why the trial was being carried out. The 1462 responses were then assessed against a framework of five key points about what the trial involved (e.g. clinical condition, trial hypothesis, intervention, outcomes, design used). The researchers concluded that trial participants are unlikely to be able to show that they had interpreted the purpose of the trial and the terms and concepts involved exactly as the researchers intended. Additional interview data with a sub-set of the women (n=20) (Kenyon et al 2006) identified that trial practices including use of placebos, randomisation, and blinding also appeared to be poorly understood.

Two further studies (Weston et al 1997, Rodger et al 2003) explored pregnant women's assessment of trial information with the view to participating in a hypothetical trial. The studies were aimed at improving trial recruitment (Weston et al 1997) and determining women's likelihood of joining a proposed trial (Rodger et al 2003). The study by Weston et al (1997) suggests that an information video combined with an information sheet may result in increasing women's knowledge of the research trial and consequently in greater participation. Rodger and colleagues (2003) tested women's comprehension of study information by interview and questionnaire. All women understood the nature of the intervention; most had a good

understanding of the risks of the intervention; however only a slim majority (57%) understood the overall purpose of the trial, the remaining women classified as having only partial understanding. However these findings do not portray real life and therefore could be misleading.

In summary, these studies give some insight into trial participants' understanding of trial information. When examining the quality of the informed consent process it has been identified that participants often have misconceptions about trials and knowledge can vary widely between participants (Ferguson 2000, Kenyon and Dixon-Woods 2004, Kenyon et al 2006). Major deficiencies in knowledge include not being aware of the potential risk associated with the trial treatment, the unproven nature of the treatment and the uncertainty of benefit to self (Rodger et al 2003, Kenyon et al 2006). The findings raise doubts about the supposition that informed consent is attainable and raise questions about whether the consent process for research has been overstated as a means of satisfying ethical imperatives and protecting the interests of participants.

2.3.5 Women appear to want to be informed about trial results; however, there is little consensus how best to do this

It might be considered surprising that clinical researchers do not routinely offer study participants the results of clinical trials. Within clinical research the intention should be to treat each individual participant with the utmost respect and as a partner in the research. In support of this approach, results should be shared, as doing so could be considered the correct course of action when working towards the common goal of partnership. Some ten years ago the Association for Improvements in Maternity Services, and the National Childbirth Trust and Maternity Alliance, in their charter for ethical research in maternity care, recommended that women should have the right to see the results of research they participated in (AIMS/NCT/MA 1997). Since the Charter was written the practice of offering results to research participants has received growing attention and is considered good practice for the ethical conduct of research. The offer to provide research results at study completion is based on the principle that respect for persons should continue

following study completion, to avoid treating research participants as simply a means to an end. Among other benefits a summary of results acts as an acknowledgement of the valuable contribution to science that has been made by their participation.

Recent government initiatives and several prominent groups in the UK have issued policy statements addressing the provision of research results. The second edition of the Department of Health's Research Governance Framework recommends that findings from research work be disseminated promptly and fed back as appropriate to participants (DH 2005). Researchers conducting research in the UK with human participants when applying for ethical approval are required at the outset to state if they will provide study results to participants following completion, as well as how they will deal with a situation where information becomes available part way through the study that may affect a participant's willingness to remain in the study (NRES 2008).

Existing written policies governing the return of research results to participants therefore promote the universal recommendation that results be offered to all research participants. The practice is promoted as a key part of ethical research, and consequentially an automatic assumption is made that providing participants with results, an intervention in itself is beneficial. These recommendations may promote researchers to provide participants with study results; there is, however, no guidance as to when and how this process should occur, adherence to the policies and format of provision being left to the individual researchers. Nor is there any recognition of the possibility that sharing research results may in fact harm participants, causing anxiety and unnecessary concern.

The potential benefits (and potential harms) of offering research results to research participants are largely unknown, despite data suggesting participants are interested in learning about study results (Elbourne 1987, Mohanna and Tunna 1999). Although the results of studies have been shared with study participants, for example in the Oracle Trial (Dixon-Woods

et al 2006) there is no systematic approach to the provision. There is currently very limited information to indicate how research participants feel about receiving research results, especially those participating in perinatal trials.

Researchers from the Oracle Trial (antibiotics for preterm labour / preterm rupture of the membranes) offered a summary of the results to the 11,154 included women (Dixon-Woods 2006). The researchers found that less than a fifth of women desired a summary of the results. A possible explanation for the modest interest shown are that those women that requested a copy of the results shortly after joining (n=1803; 20%) were required to re-confirm they still wished to receive them once the trial was complete (n=1524; 17%). The trialists then assessed the participants' reactions by conducting qualitative interviews with 20 of those who received the summary. Reactions to receiving the results was generally positive or neutral, although some women had difficulty understanding the leaflet, and there was evidence of possible negative implications for women who had adverse outcomes. Women appeared to request the results because they were interested in being able to complete their own personal trial participation journey. They wished therefore to know to which arm of the trial they had been allocated and the implications for their own pregnancy, and they were disappointed in receiving a generic summary. Individualised results for example unblinding, and communication of summary findings may be separate issues to researchers, but participants are unlikely to make this distinction.

2.3.6 Women's personal accounts of participating in perinatal trials

Women's personal accounts of joining trials that demand intrapartum consent give some valuable insight into the trial experience. For example, Moran (1993) describes the difficulty she was faced with when considering joining a trial whilst in preterm labour with twins. She was offered participation in the pilot study that preceded the Oracle Trial (antibiotics for women in preterm labour or with preterm rupture of the membranes). She acknowledges that participating in the trial ensured she was given all the available choices and treatment options. She relates a feeling of altruism after joining; but at the

time her concern had been for her unborn babies and she felt the possible benefits of the antibiotics outweighed any potential risks.

Some women will want to know about all the possible risks associated with pregnancy and research being conducted that they may potentially be eligible to join, while others may not wish to know about such risks prior to them taking place. Sudlow (2005) presents a conflicting picture regarding the ethical issues she was faced with when considering consenting to a trial. A neurologist and clinical researcher herself, she describes her reaction when moments before undergoing a caesarean section, a research nurse sought her consent for a trial. Taking part in the trial required some umbilical cord blood being taken from her placenta after delivery for stem cell research. Before signing the consent form it was obligatory for her to read the one page leaflet and respond to several questions about her understanding of the trial. Although not unwell and having a medical background, she found she had to concentrate fully in order to understand the leaflet. At first she thought she was being asked for some of her baby's blood and wanted to know more about the risks. Once she appreciated that the blood was to be taken from the placenta prior to disposal and not from the baby, making (in her view) the research entirely non-invasive and not at all harmful, she was more than happy to sign, and did so feeling that she need not have been asked at all.

Sudlow argues that the consent procedure was designed simply to satisfy the research ethics committee; the process of gaining her consent was an unnecessary intrusion and increased her own anxiety, and as a result it was the only harmful part of the trial. She argues that (in a heightened emotional state) had she misunderstood what was being asked of her and so refused consent to the study the placenta would have been needlessly discarded, without the sample of blood being taken. The need for consent, she states, did not protect any right she may have had for the cord blood to be discarded when something useful and non-harmful could easily come out of it. And, if research is publicly funded, she asks what about the rights of taxpayers not to have their money wasted on a process that increases costs because of the additional resources needed to seek and document consent; and that

prolongs the research because of the wastage of samples where no consent is obtained. This account highlights the difficulty associated with giving the appropriate amounts and type of information to potential trial participants. Different women will require different amounts and type of information. Some women may wish to know the full details of a research trial and what their involvement will mean, whilst others may wish to know very little.

Washington (1995) in her account describes a time when she refused to give her consent to having an intrauterine pressure catheter inserted to measure contractions. She refused to participate in the research as she was under the impression that the obstetrician thought she was not in labour: She also questioned how effectively she would have taken in information about possible risks and given 'informed' consent in this situation.

These various studies and personal accounts indicate that there is a significant deficit in current understanding about the need for the provision of research results to participants. Existing standards and empirical research provide little guidance. The potential for extreme and negative responses to trial results means that communication constitutes an intervention in its own right. It therefore requires appropriate evaluation. While government initiatives, users, and research ethics committees are generally supportive of the concept, the needs and attitudes of participants are relatively unknown. It is difficult to determine from the ten empirical studies identified in the literature review how many, if any, provided their participants with the study results. It seems reasonable to assume that the trials did not have any policy on providing results to the participants, as they would, presumably, have demonstrated this had it been the case. To date, there is little published evidence to suggest either positive or negative outcomes of sharing perinatal trial results.

Table 2.1 Characteristics of empirical studies

Trial	Reference(s)	Summary of original trial	Summary of participants	Findings
Newbury Maternity Care Study (UK)	Elbourne 1987	RCT of carrying hand-held maternity notes - antenatal period	Women recruited to Newbury Study sent postal questionnaires at 4 time points. The final questionnaire (6 months postpartum) included 1 open-ended question about trial experience. Thematic analysis of free text responses performed. Response rate: 92% (n=247).	Altruism key to joining. Women wished to know the trial results.
FOREMOST Trial (Australia)	(i) East 1996, (ii) East 2006	RCT of fetal monitoring device & CTG versus CTG only - in labour	(i) Women recruited to FOREMOST Trial were given a questionnaire and whilst on the postnatal ward. Women were asked to rate their trial experience (1 fixed response question - poor, fair, good, excellent). Response rate 99% (n=77). (ii) 2nd postal questionnaire incorporating 3 questions relating to trial experience. Given on postnatal ward, & repeated 3 months later. Questions with same fixed response options, plus space for comments. Response rate: 1st Q - 75% (n=448), 2nd Q – 54% (n-318).	(i) Women rated their participation favourably (44% good, 55% excellent). (ii) Women rated their participation favourably. Altruism key to joining. Would have preferred to be informed antenatally about FOREMOST trial.
Term PROM (Canada)	Weston 1997	Trialists evaluating the effect of Term PROM trial information video (RCT of management policies for rupture of membranes at term). Women included in video evaluation study were not eligible for Term PROM Trial, therefore situation hypothetical - antenatal period.	Women randomised to receive written information & watch video about Term PROM Trial (n=42) or written trial information only (n=48). Questionnaires asked about willingness to participate in trial (in the hypothetical event should they become eligible) & assessing understanding of trial. Questionnaire completed immediately after intervention and repeated 2-4 weeks later. Response rate: 1st Q - 100% (n=90), 2nd Q – 94% (n=85).	1st questionnaire – more women likely to participate in Term PROM trial if watched video. No difference in knowledge in either group. 2nd questionnaire – no difference in likelihood of participation in either group. Trial information was better retained in the video group.

Trial	Reference(s)	Summary of original trial	Summary of participants views study	Findings
PLANET Trial (UK)	Mohanna and Tunna 1999	RCT – of nifedipine versus placebo to prevent onset of pre-term labour – antenatal period	Women considered high risk of pre-term labour were invited to participate in the PLANET Trial. Those declining participation were interviewed (2 years after invited to PLANET Trial). Response rate: 6% (n=18).	Reasons for declining participation: chance of receiving a placebo (wanted the drug), women told antenatally about the trial and could not see the relevance to them, needed more time to consider.
Analgesia Trial (UK)	Ferguson 2000	Qualitative study exploring views of 104 participants who had taken part in 14 different drug trials. Includes 26 women in a Phase III labour analgesia trial.	Structured interviews exploring views of 104 participants who had taken part in 14 different drug trials. Comparison of the views of 26 women in the labour analgesia trial with those (n=78) recruited to the other 13 trials. Interviews explored understanding of trial, satisfaction with information, and reasons for participating (12 months after joining).	Women in labour drug trial were less satisfied than those recruited to the other trials, they reported lower levels of understanding; they asked fewer questions and reported lower levels of satisfaction with the answers.
MLAC Trial (USA)	Dorantes 2000	Observational study of epidural analgesia (using minimum local analgesic concentration (MLAC)) - in labour.	Women requesting an epidural were invited to participate in MLAC Trial (n=294). Regardless of whether they participated, women were subsequently asked to complete questionnaire detailing their reasons for their decision. Two questionnaires were used; 1 for those agreeing to participate in MLAC and 1 for those who declined. Response rate: agreeing 60% (n=166), decliners 40% (n=109).	Self-benefit key to joining, then altruism. Decliners more likely to consider side-effects and risks.
TIPPS Trial (Canada)	Rodger 2003	Questionnaire based study evaluating women's willingness to participate in a hypothetical RCT (TIPPS Trial - comparing heparin with placebo as a prevention for thrombophilia in pregnancy) - antenatal period.	Women were provided with written information describing the TIPPS Trial. Women were asked if they would be willing to participate in TIPPS in the hypothetical event should they become eligible. Questionnaire comprised 3 questions: 1-willingness to participate (fixed response options given: yes or no), 2-open ended question re factors influencing decision-making, 3- reasons for agreeing / declining participation (5 fixed response options). Response rate: n=50.	Women rated yes willing to participate (74%). Benefit to child (68%), self (27%), altruism (5%) were key to joining.

Table 2.1 Characteristics of included studies continued

Trial	Reference(s)	Summary of original trial	Summary of participants views study	Findings
Twin Birth Trial (Canada)	McLeod 2004	Questionnaire based study evaluating women's willingness to participate in a proposed RCT (vaginal birth versus caesarean section for twin delivery) - antenatal period.	Women were provided with written information describing the Twin Birth Trial. Women with a twin pregnancy were asked if they would be willing to participate in the proposed Twin Birth Trial. The questionnaire asked about willingness to participate in proposed trial (fixed response options given: yes, no or not sure). Additional free text to explain their answer re factors influencing decision-making. Response rate: n=64.	Women rated yes willing to participate (48%), not sure (22%), & no (30%). For those stating yes: (90%) altruism was key to joining. 36% of those not sure wanted to speak to their partner. 63% responding no stated they preferred a vaginal delivery.
ORACLE Trial (UK)	(i) Kenyon 2004, (ii) Dixon-Woods 2006, (iii) Kenyon 2006	RCT of antibiotics versus placebo – in preterm labour +/or premature rupture of membranes	(i) Women recruited to ORACLE Trial were sent postal questionnaire to assess trial understanding (1 month after recruitment to ORACLE. Response rate: 61% (n=1875). Content analysis of free text responses was performed. (ii) & (iii) Follow up in-depth interviews exploring reactions to receiving trial results and trial experience with 20 of these same women (up to 4 years after joining).	(i) Full understanding of trial purpose & design not evident. (ii) Reactions to receiving results generally positive, although some women had negative implications. (iii) Self-benefit key to joining, then altruism
Maternity research (UK)	Baker 2005	Qualitative study exploring views of 17 women who had agreed or declined participation in different studies whilst pregnant	Focus groups (12 women that had not declined any research) and semi-structured interviews (5 women that had both agreed & declined research participation) - (6 -12 weeks postnatal). Response rate: 13% (n=17).	Altruism and self-benefit both key to joining. Decliners identified the timing of the approach to participate was inappropriate, they felt vulnerable and unable to believe clinical equipoise existed.

The remainder of this chapter is divided into sections reflecting the different issues participants can be presented with when considering joining a trial. Comparisons are made between the situation that women were in when asked to consider joining the Magpie Trial and situations experienced by those taking part in trials in other areas of health care not related to pregnancy (for example the experiences of those having to make decisions to join whilst in a critical care situation and those faced with considering joining oncology trials). Although not fully applicable to pregnancy, these studies do provide useful insights; as do trials where considerations for a third party (newborn) was necessary. The review concludes with literature exploring trial participants reactions to the methods used within randomised trials. This literature is relevant in order to appreciate the women's understandings of the Magpie Trial and is applicable to the analysis and interpretation of the QUOTE study findings.

2.4 Trials involving an emergency situation

Consent to join a trial while in a clinical emergency situation can be required in a number of settings, including accident and emergency, anaesthesia, or prior to surgery. Studies taking place in accident and emergency settings include conditions that involve a severe trauma; such as head injuries (Foëx 2001), cardiac arrest, acute stroke, congestive heart failure, sepsis, haemorrhage or a drug overdose (Passamani and Weisfeldt 2000). In these types of circumstances the nature of the condition may undermine the capacity of the patient to consider joining a trial. This will be compounded by feelings of vulnerability and anxiety while undergoing unforeseen urgent treatment, likely similar to the feelings experienced by women with severe pre-eclampsia (Redman and Walker 1992:157).

One such situation was explored by Williams and colleagues (2003); who evaluated informed consent to a research trial for the treatment of acute myocardial infarction. Consent was required at a time when worry, fear, pain and treatment with morphine might have compromised the ability of patients to comprehend information about the trial and give informed consent. The study assessed whether patients could understand the written and oral

information given to them and whether they were competent to give autonomous informed consent to participate in the trial. The study included 399 patients with acute myocardial infarction in 16 hospitals in New Zealand and Australia who were eligible for participation in the Hirulog and Early Reperfusion or Occlusion (HERO) -2 trial of two antithrombin regimens (bivalirudin versus heparin) administered adjunctively with streptokinase. All participants were asked whether or not they had read the trial information sheet. The questionnaire aimed to capture self-reported comprehension of the oral and written information they were provided with. Only 63 (18%) had read the trial information leaflet before giving or refusing consent to participate. Patients who gave consent (n=367) were more likely to report good or partial comprehension of the information provided than were those who refused consent (n=32): 272 (74%) versus 14 (44%), respectively. In an assessment of competence to make an autonomous decision, 75 of 145 (52%) were ranked at the lowest grade and 26 (18%) were considered not competent to consent. The authors of the study acknowledged that little is known about factors that affect patients' decisions to give or decline consent to clinical trials and that although the consent process for HERO-2 met regulatory requirements for clinical trials, it was inappropriate for the needs of most patients. They conclude the patients' comprehension of the information provided and their competence to autonomously give consent was less than optimal.

Other empirical research (Montgomery et al 1996, Yuval et al 2000, Gammelgaard et al 2004a, Gammelgaard et al 2004b, Demarquay et al 2005) has confirmed the finding that participants' comprehension of research trials in highly stressful situations may be sub-standard. Participants reported that they felt pressurised to take part in trials, in the sense that they were approached at a time (before major surgery) when they had felt vulnerable and stressed and considered they were not really capable of making a decision (Montgomery et al 1996). In one study less than a third fully comprehended the trial, the majority reporting having only partial or no understanding at all (Yuval et al 2000). In one study (Gammelgaard et al

2004a) participants failed to understand they had consented to a randomised trial but believed they were consenting to routine medical treatment.

Clinicians acknowledge the problems faced with the issue of consent in emergency medicine research (Lindley 1998, Anon 1999, Foëx 2001, Verdú-Pascual and Castello-Pone 2001, Satchithananda et al 2001, Lötjönen 2002, Schmidt et al 2004). Schmidt et al (2004) acknowledge that the emergency setting presents unique barriers to informed consent both because of the time frame in which the research is performed and because patients in the emergency department are a vulnerable population. Informed consent by the patient is always preferred to consent by a representative or, exceptionally, to waiving consent altogether; it follows that the information given to the patient in urgent circumstances should be particularly concise and understandable. Therefore, the focus of informing the patient in a very anxious state should be on the core elements: the purpose and nature of the intervention as well as its consequences and risks (Lötjönen 2002).

An exception to the requirement of prospective informed consent, a waiver of informed consent in acute emergency situations, has been long awaited by emergency care researchers (Baren et al 1999, Biros et al 1999, Crash Trial 2004, Shakur et al 2007). An amendment of the UK's Medicine for Human Use (Clinical Trials) Regulations 2004 came into force in 2006. The amendment allows unconscious patients in emergency situations to be enrolled in clinical trials without prior consent, provided that the appropriate ethics committee has approved this.

2.5 Trials involving making a decision on behalf of a third party

Neonatal and paediatric research provides interesting examples of where parents have been required to consent for their baby; the baby is often very ill, there is usually clinical urgency, and the situation can be compounded by great parental distress (Modi 1998, Elbourne et al 2001, Cooke 2005). Neonatal (up to 28 days after birth) trials generally involve highly complex medical issues; mothers are commonly affected by a combination of blood loss, pain, exhaustion, and potent medications; and in many cases both

parents are under profound emotional distress because of serious illness or malformation of the baby (Tyson and Knudson 2000). The parents' consent is often requested whilst their baby is under the care of the clinician making the request. Parents' may feel powerless, their medical knowledge may be poor, and they may not understand the complex medical arguments put to them. Parallels can therefore be drawn from the accounts of parents in these situations with the situation of those joining the Magpie Trial. Concern has been raised regarding methods used for obtaining consent for neonatal research, as these are not circumstances best suited to understanding the need for, as well as the nature of, clinical research. The inevitable time constraints compromise understanding and voluntariness, which are essential components of adequately informed consent (Modi 1998, Nicklin and Spencer 2004). Furthermore, evidence suggests that parents do not always fully understand the research process (Anon 1995, Levene et al 1996, Zupancic et al 1997, Stuijvenberg et al 1998, Anon 1999, Allmark et al 2001, Campbell 2001, Stevens and Pletsch 2002, Kupst et al 2003, Ballard et al 2004, Dawson and Spencer 2005, Eiser et al 2005, Hoehn et al 2005, Kassam-Adams and Newman 2005).

Mason (2000) reports the views of neonatologists and parents who gave consent for their baby to be entered into a trial and those who declined. Views were collected from 107 neonatologists and the parents of 200 infants in nine UK counties using semi-structured interviews. Assessments were made of the information provided, parental understanding, parental competence, and voluntary nature of the consent. Interviews with parents revealed that there had been problems with each of these four components in 10-22% of consents sought. The parental interviews also revealed that in more than two-thirds of all consents sought there had been a problem with at least one component. This percentage was three-fold greater for trials of emergency therapies than for trials of non-urgent therapies. Nevertheless, parents highly valued the consent process. Neonatologists in contrast seemed less convinced of its value; their responses were perhaps influenced by the belief held by 47% of them that the requirement to obtain informed consent sometimes prevented useful neonatal research. Consequently

researchers were reluctant to approach parents who were in any way distressed, because of the difficulty in ensuring consent (Mason 2000).

Evidence from other studies has identified a significant proportion of parents who, give written consent for a trial in the early neonatal period, do not later remember having done so (Snowdon et al 1997, Elbourne et al 2001, Ballard et al 2004, Nicklin and Spencer 2004, Stenson et al 2004). Once the trial is underway, some mothers experience regrets and self-recriminations about their decision to consent (Stevens and Pletsch 2002). Concerns have also been expressed regarding extremely high consent rates (Campbell 2001; Stenson et al 2004), parents being more likely to consent to a trial when their infant was critically ill soon after birth than they were a week later (Levene et al 1996). This could be explained by the fact that parents are so anxious about the welfare of their newborn that they are not 'consent competent' and their consent may not be truly voluntary (Burgess et al 2003), nor will they be able to understand complex medical information; hence their consent/permission will not be appropriately 'informed' (Anon 1995).

The parents of 199 infants entered into a randomised trial of pulmonary function testing were sent a short questionnaire eighteen months later to investigate their recollections of consenting and to determine their views about the need for consent (Stenson et al 2004). By enrolling their infant in the trial, 12% thought they might get better care. A quarter of parents became more anxious regarding their infants' condition after having the trial explained to them. Explaining the trial necessitated a detailed description of the baby's condition and introduced medical uncertainty about the optimal treatment. Clinicians acknowledged that obtaining fully informed consent placed extra emotional burden on them too.

Other examples of exploring the views of parents who have consented their critically ill newborn baby have identified important issues relevant to those concerned with trials (Snowdon et al 1997, 1998a, 1998b). Snowdon et al (1997) interviewed the parents of 21 infants who were enrolled in the ECMO (Extra Corporeal Membrane Oxygenation) trial. They found that some

parents were unsure whether their babies were in a trial or not and the nature of the trial was often poorly understood. The random basis of the allocation of treatment and the rationale behind this approach were also problematic issues. Some parents did not perceive a random element in the process at all. The same authors (Snowdon et al 1998a) extended their work by assessing the views of parents about receiving the ECMO trial results. Information about mortality was well understood by the parents, but morbidity was less clearly understood. Even when the content was emotionally exacting, the information was still wanted, as it removed uncertainty; provided an endpoint to difficult events; promoted further discussion within couples; and acknowledged their contribution to answering an important clinical question. The parents in this study thought that participants of a trial should be provided with the results.

An earlier account from one of the parents involved in the ECMO Trial describes her decision to refuse consent for her son to enter the trial. Blewitt (1994), a midwife herself, was asked to consider consenting her son born with persistent pulmonary hypertension of the newborn and requiring ventilation. The trial was presented as her baby's last chance. Both parents felt certain their son would die so the trial seemed to offer only a prolongation of the situation. Their decision to reject the trial, described as the hardest decision of their lives, was made to preserve their son's dignity and prevent further suffering.

Snowdon and colleagues (2007) furthering their work interviewed five parents (two couples, one mother) who declined to enrol their baby in the CANDA Trial (comparing two forms of a lung expander compound given shortly after birth to very premature babies). The declining parents saw no intended or likely benefit from participating, but an over-stated sense of risk and threat. The authors term this flipside to the therapeutic misconception as 'injurious misconception'.

This appropriateness or otherwise of burdening parents with the additional responsibility of decision-making at a time of great psychological stress

warrants further consideration. Mason (1997) recognises the additional stress the process of consent can place on parents, but balances this against the need for randomised trials in order to improve clinical care. Others have suggested use of the Zelen (1979) design, in order to minimise the stress caused by asking frightened and confused parents to make complex decisions (Anon 1995). This alternative to the consent process was explored by Snowdon et al (1998b). Parents of surviving infants enrolled into the ECMO trial were interviewed to find out their views on the concept of Zelen randomisation. It was proposed that in a trial such as ECMO, written consent would be sought only if the baby were to receive ECMO; thus avoiding further distress to already frightened parents by asking them for written consent for randomisation and conventional ventilation. More parents of infants not randomised to receive ECMO considered it unacceptable than did parents of infants randomised to ECMO, indicating that those who it aimed at protecting generally rejected the Zelen approach. There is, however, evidence that people have difficulties with the consent process outside research situations (Habiba 2000). When asked to compare information they received as a clinical trial participant with the information they generally were given as a patient, Ferguson (2002) (previously discussed) showed that in general patients do receive more information when participating in trials.

2.6 Adequacy of trial information

It is evident from the literature (Chalmers 2003, Kenyon and Dixon-Woods 2004, Snowdon et al 1997) that uncertainty exists about what research participants ought to understand about the purpose of clinical research. There is some consensus that they should understand that research has scientific goals. However, there are differences regarding what should be understood about the goals of research and whether these goals involve potential for clinical benefit (Henderson et al 2007). The lack of appreciation that proposed treatments are not always beneficial and interpretation of the research intervention as a true therapeutic option was first described by Appelbaum (1982) as 'therapeutic misconception'. Appelbaum and colleagues (1982, 1987) report the findings from case studies of two psychiatric research projects: the first examining the effect of social skills

training for people with chronic schizophrenia (non-randomised), and the second addressing the efficacy of two medications for the treatment of personality disorder (randomised). In examining the participants' understanding of the respective projects, the researchers concluded participants from both judged the research interventions to be assigned on an individual basis, based on the patient's particular need, sometimes by fabricating a therapeutic basis for the process. For example, they believed allocation was based on either: each person needing different treatments, the patients' 'thinking capacity', how they performed in the consent interview, their mental ability, or IQ score. Although some patients did state the trial treatment was by random allocation, they too were unable to accept this was so in their instance, and preferred to believe their trial treatment was based on their own clinical need.

Informing parents antenatally about the possible need for emergency neonatal research, with presumed consent and scope for opting out, would possibly address these problems. It would spare parents of sick neonates, already terrified by their baby's illness, further distress (Manning 2000). Another way of improving this process is to ensure that when parents give consent, they also get a leaflet that summarises the trial and indicates who they could contact if they have further questions (Goodare and Williamson 2001; Tarnow-Mordi 1999). As well as including provision of information about appropriate trials before delivery, there would also be more time for reflection (Burgess et al 2003; Dawson and Spencer 2005). The presence of a nurse at the time of information giving has been strongly associated with parental understanding (Kodish et al 2004). However, as previously discussed, informing potential participants of research is not without its difficulties.

Many studies have examined the type of written and oral information provided by researchers about trials and how participants make sense of this information. Examples of oncology trials were explored by Bjørn et al 1999, Fallowfield et al 1998, Featherstone and Donovan 1998, 2002, and Jenkins et al 1999. Jenkins and colleagues (1999) audio-taped discussions between

doctors and patients in which consent was being obtained, in order to evaluate the type of oral information presented to trial participants. Eighty-two discussions conducted by five clinical oncologists took place. In most cases (96.3%) describing that uncertainty exists about treatment decisions was discussed. In almost every case it was in a general sense (95.1%), but some clinicians mentioned personal uncertainty (14.6%). The process of randomisation (in 95.1%), treatments (in 82.9%) and possible side effects (in 87.8%) were described frequently. An area of concern was that no written information about the trial was given to over a quarter (28%) of participants, no explanation by the trialists being given in the report. The majority of patients (85.4%) raised general questions about the trial, ranging from a fear of being experimented on to reservations that one of the treatments may be inferior to the other. In addition nearly half (46.3%) of the patients specifically questioned the potential side effects of treatments, not a surprising finding given the research was on oncology. The researchers conclude that UK clinicians adopt individual methods when providing information and soliciting consent to trials.

Another study from which evidence was gained involved women with breast cancer randomised in a trial of adjuvant therapy (Hietanen et al 2000). A questionnaire was developed to inquire about the adequacy of the oral and written information given prior to recruitment. Information provided was regarded as easy or quite easy to understand by 91% (1231/255) and adequate for decision-making by 72% (184/254) of the women, while 15% (37/254) had found it less than adequate and 4% (10/254) very insufficient. For 55% (125/226) of the women written information had been helpful for decision-making, while 7% did not find it helpful, and 8% women could not remember having received the written information. For 7 women (3%) the doctor did not explain anything about the trial. Sixty-eight percent of women thought they had enough time for decision-making while 17% would have liked to have more time.

Uncertainties therefore exist as to the best way of presenting trial information. Marteau (1994) in a letter to the British Medical Journal proposes that when

there is behavioural uncertainty, such as over how to inform participants about trials, randomised trials should again be the research method of choice for resolving it. Such studies would compare the effects on different groups of participants of different methods of informing them about trials. These methods could vary in the amount and type of information provided, the training of the person providing the information, and the period over which information was given and decisions sought. The impact of these different approaches on emotions, cognitions, and decisions could be assessed.

Subsequently Aaronson et al (1996) evaluated the impact of information provision on trial participation in a randomised trial. One-hundred and eighty patients who were approached to participate in a cancer trial were randomised to a standard informed consent procedure based on oral explanations from the treating physician plus written information or the same plus a follow-up telephone call from an oncology nurse for a further discussion of the trial. Face-to-face interviews were performed a week later to evaluate the intervention. Patients receiving the extra discussion were better informed than the standard consultation group about the clinical trial, the voluntary nature of participation, the randomisation process, the right of withdrawal and treatment alternatives; and were no more anxious than the standard group. However the intervention had a negative effect on accrual, as this group was also more likely to decline trial participation (13% versus 24%).

More recently, a systematic review by Flory and Emanuel (2004) of interventions to improve research participants' understanding of informed consent for research concluded that efforts to improve understanding through the use of multimedia and enhanced consent forms have had only limited success. Having a study team member or a neutral educator spend more time talking one-on-one to study participants appears to be the most effective available way of improving research participants' understanding of a trial; however, the authors concluded further research is needed. Conclusions were based on a review of 30 studies describing 42 trials. Of 12 trials of multi-media interventions, three showed significant improvement in

understanding. Of 15 trials of enhanced consent forms, six showed significant improvement in understanding, but 5 of the 6 were of limited quality, casting doubt on their practical relevance. Of five trials of extended discussion, three showed significant improvement of understanding and two showed trends toward improvement. Of five trials that tested participants' knowledge about the trial, all showed significant improvement in recall, but were potentially flawed in that they may have mistaken rote memorisation for improvement in understanding. The remaining five trials had varying impact on understanding. Three showed a significant increase; two using extended discussion and one where participants underwent some research protocol procedures before deciding whether to give consent. The remaining two interventions did not show a significant increase in understanding. The authors also identified that lower education was associated with less understanding. Satisfaction and willingness to enrol were never significantly diminished by any of the interventions.

Such educational efforts to improve the understanding of prospective clinical trial participants are being addressed, perhaps unintentionally, by the National Curriculum (Education Reform Act 1988). For example science at key stages 1 and 2 (year 3 and 4, ages 7-10 years) children are being taught the attributes of a 'fair test', which focuses on the design issues, which underlie the purpose of scientific experiments. This could possibly produce substantial improvements in prospective trial participants' understanding of the key elements of scientific design.

2.7 Participants' understanding and reactions to trial design

The scientific justification for the basic principles of trial design: equipoise, allocation concealment, randomisation, use of placebo and blinding has already been described in a previous chapter. Here consideration is given to the relevant literature describing how trial participants are presented with these overlapping concepts and what understanding they attach to them. This evaluation will give an insight into the women's experiences of the Magpie Trial.

2.7.1 Equipoise

An ethical cornerstone of the randomised trial is that it should only be carried out when the effects of the intervention are unclear. This state of genuine unknowing regarding the comparative therapeutic merits of treatments in each arm in the trial is termed 'equipoise' (Freedman 1987), and means that the level of uncertainty is such that there is no preference between treatments (Sackett 2000). Uncertainty therefore is a moral prerequisite for a controlled trial; if we know what we should do, we should do it, not study it (Enkin et al 2000). Freedman (1987) challenged the idea that an individual clinician must be in a state of complete indifference with regard to two alternative treatments in order to randomly assign patients to those treatments, suggesting this as an untenable situation. The alternative concept he suggests is "clinical equipoise", being satisfied that there is genuine uncertainty within the expert medical community as a whole, and not necessarily on the part of the individual investigator about the preferred treatment (Freedman 1987).

The concepts of individual equipoise and collective equipoise have been frequently discussed (Chard and Lilford 1998, Shapiro and Cranley Glass 2000, Weijer et al 2000, Lilford 2001). Individual clinicians who lack personal equipoise are advised to accept clinical or communal equipoise, based on current unresolved disagreement among the medical profession (Alderson 1996). Lack of individual equipoise should not be taken to mean that it is not therefore reasonable for an individual clinician to join a clinical trial.

Sackett (2000) proposes that the 'uncertainty' principle (individual equipoise) acknowledges that most clinicians and patients do have hunches about a treatment's effectiveness, but are 'uncertain' about whether their hunches are correct. Clinical (collective) equipoise, he proposes, permits individual clinicians and patients to have hunches as long as they recognise that colleagues whom they consider responsible and competent prefer their less-favoured treatment. Fergusson and Herbert (2000) continues the argument by stating that clinical equipoise, unlike uncertainty can never be "possessed" by individuals. It is a collective concept, it allows for genuine uncertainty at

the level of the medical community to coexist with the possibility of uncertainty at the individual level.

Published literature suggests trial participants often show signs of misunderstanding the basis of their treatment allocation, and assume that one treatment is already known to be better than the other or others (Snowdon et al 1997, Mohanna and Tunna 1999, Featherstone and Donovan 2002, Mills et al 2003, Robinson et al 2004). However it is not clear from the literature if potential participants are given the correct information by clinicians in order to have a full appreciation. Participants may expect clinicians to assign them to treatment based on their specific symptoms, clinical findings, and age rather than at random (Featherstone and Donovan 1998).

Participants themselves also have preconceptions about the relative merits of the study treatments (Lilford 2003). Participants may have joined trials in the hope of better personal treatment accruing by nature of receiving the experimental arm of the trial (Halpern 2003; Welton et al 1999). Alternatively treatment preferences among participants have been shown to decrease their willingness to enrol (Baker et al 2005; Jenkins and Fallowfield 2000). Robinson at al (2004), evaluating the lay public's understanding of equipoise, concluded that the public have difficulty in accepting the possibility that a doctor could be completely unsure about the best treatment. One such example is provided by Toynbee (1997). On hearing the background trial evidence she chose her treatment, rather than agreeing to be randomised; the decision was made on the basis it was what her doctor thought was best, even if he didn't know it for sure.

Failure to understand clinical uncertainty could occur if trial information is too complex for the patient to comprehend, or if the patient is not given sufficient time or opportunity to take it in (Robinson et al 2004). The United Kingdom's National Research Ethics Committees (NRES 2008) suggest the following wording for information leaflets given to the participants of trials: "Sometimes

because we do not know which way of treating patients is best, we need to make comparisons" (NRES 2008).

Surveys also indicate that clinicians involved with trials commonly have treatment preferences (Alderson 1996). Fear of damaging the relationship with the patient and losing the patient's trust has been identified as a reason for doctors being reluctant to admit publicly that they do not know which treatment is best (Jenkins et al 1999; Ross et al 1999). Donovan et al (2002) in their study explored interpretation of study information and factors effecting recruitment. They found that recruiting clinicians had difficulty discussing uncertainty and presenting treatments equally. In a later report the same group of researchers confirmed this finding in that only if patients could accept that the clinician was in genuine uncertainty was randomisation seen as acceptable (Mills et al 2003).

In order to understand the concepts of equipoise and uncertainty from the perspectives of those directly involved, professional care-givers involved in a neonatal intensive care trial were interviewed (Garcia et al 2004). Almost all neonatologists used the concept of equipoise in their interview. They explored ideas about equipoise at the individual and collective levels. Feelings of doubt about a trial and disturbed equipoise were more often expressed by more junior doctors.

2.7.2 Randomisation

From a trialists' perspective the state of initial equipoise that motivates setting up the trial also provides the ethical justification for randomisation (Robinson et al 2004, 2005). Random allocation of participants to treatment arms is widely considered to be the best way of achieving results that genuinely increase knowledge about treatment effectiveness. Despite the widespread use of randomisation, its centrality to the scientific method and the controversy which results from its use, little attention has been paid to participants' reactions to and understanding of this aspect of their trial experience (Snowdon et al 1997).

Giving complex information to participants about trials and describing the concept of randomisation in simple terms has been identified as the primary difficulty for clinicians involved in trials (Fallowfield et al 1997). In a study that examined the standard of consent used by clinicians in European randomised clinical trials, 38% of clinicians reported that they did not always tell patients that they had been assigned to their treatment randomly (Williams and Zwitter 1994). It follows then that understanding the concept of randomisation can also be difficult for the individual patient to comprehend (Edwards et al 1998). There are suggestions that members of the public see no scientific benefit to randomisation (Robinson et al 2004), and it has emerged as being a major barrier to recruitment (Fallowfield et al 1998). A fear of randomisation, together with wanting the doctor to choose the treatment, can be reasons for declining trial participation (Llewellyn-Thomas et al 1991, Jenkins and Fallowfield 2000).

Hietanen et al (2000) reviewed what was understood by participants randomised in a trial of adjuvant hormonal therapy for breast cancer. While all participants were aware they were in a clinical trial and most were satisfied with the information they received, the method of treatment allocation was unclear to most. Over half of those interviewed thought the doctor had chosen the treatment. Evidence from another study supports this finding (Pope et al 2003). Participants preferred to believe that investigators knew which treatment they were receiving, and had made a good decision specific to their case, despite having been told about concealed allocation and placebo use.

Participants often struggle to understand the reasons for randomisation (Featherstone and Donovan 1998 and 2002) and often fail to grasp the random basis of the allocation of treatment and the rationale behind this approach (Snowdon et al 1997). Participants have given rationing of scarce resources as the reason why randomisation is used (Snowdon et al 1997, Featherstone and Donovan 2002). For example, in Snowdon's study some parents of seriously sick infants assumed that randomisation was used to

decide which babies might have access to the limited number of places at centres where the experimental treatment was available.

One study exploring the preferred wording to explain the concept of randomisation has been undertaken (Corbett et al 1996). Participants were the general public, medical secretaries and medical students. Of the seven descriptions of randomisation used in the study, two were clearly disliked by most of the people interviewed. Both of them explain randomisation in terms of either "drawing names out of a hat", or "tossing a coin". The clear favourite explanation made no attempt to explain how chance would result in treatment allocation. The researchers conclude that preferred wordings are less explicit and allow the mind not to dwell too long on the random nature of treatment assignment or the loss of medical control.

Jenkins and colleagues (2002) report the results of a questionnaire-based survey, using the seven descriptions of randomisation from Corbett's previous work (Corbett et al 1996). Participants were the general public, patients with cancer and oncologists. Complementing Corbett's results the statement 'tossing a coin' was strongly disliked by all groups of participants. The statement 'once you have agreed to enter the trial, you will be allocated to one of two treatments with equal chances of each treatment being the one you will receive' was chosen by clinicians as the closest reflection of their own practice. Older participants and women participants preferred this statement but younger members of the public disliked it.

The recommended narrative for 'random allocation' given to researchers by the UK NRES encompasses the International Conference on Harmonisation document on Good Clinical Practice Guidelines. Researchers are directed to use the wording: "People will be put into groups and then compared. The groups are selected by a computer, which has no information about the individual – i.e. by chance. Participants in each group then have a different treatment and these are compared." Researchers are advised to tell the participants what chance they have of getting the study drug/treatment e.g. a one in four chance.

2.7.3 Placebo and blinding

Evident from the literature is the lack of discussion or empirical research evaluating understanding participants have of the role of placebo and blinding in trial design. In placebo controlled trials, participants are told they may receive a placebo; this is usually described as a harmless inactive substance or an inactive dummy drug (Blasi di et al 2005). Little is known about whether the prospect of receiving a placebo influences willingness to participate. A qualitative study evaluating participants' motivations and concerns regarding joining a hypothetical trial of a new antihypertensive drug found that a quarter of all participants would decline participation because of the possibility of receiving a placebo (Halpern 2003). This finding compliments an earlier study by Welton and colleagues (1999), which indicated that inclusion of a placebo arm in a clinical trial of hormone replacement therapy reduced some women's stated willingness to participate. Women stated explicitly that they did not wish to take a placebo and expressed unease at not knowing which tablet they would be on (Welton et al 1999).

2.8 Conclusion

This literature review goes some way to understanding the perspectives of participants in clinical trials. It is against this background that the research question that is the focus of this thesis evolved. Despite the ongoing interest and concern about informed consent in clinical research, there remains little empirical work specifically exploring trial participation of those in perinatal trials. Even less work has explored the views of women being faced with trial participation whilst experiencing a pregnancy related illness. Reviewing the literature pertaining to the experiences of those recruited to trials in situations other than pregnancy, although not completely generalisable, provides useful insights. Much of the evidence is derived from specific patient groups and therefore it could be argued these trial participants (sick patients) have different relationships with their carers than do pregnant women. However, the women recruited to the Magpie Trial were also experiencing an (pregnancy related) illness suggesting useful parallels can be drawn. The findings of the review identified the problems and difficulties participants may

face when considering joining a randomised trial. However, as identified there is a scant amount of research that focuses on pregnant women as a distinct group, or gives guidance as to understanding their experiences of trial participants.

Areas needing to be further addressed appeared to be: participants' understanding of the purpose of research, views about the nature of research, reasons for joining, whether any pressure to join is experienced, and the involvement of others in decision-making; as well as evaluation of understanding of the written and oral information provided at the time of recruitment. The issues of understanding of trial methodology, in particular the concepts of equipoise, randomisation, and blinding, needed exploring also. The literature review revealed that these questions had yet to be formally addressed from the perspective of the pregnant woman.

The rationale for the QUOTE Study was, therefore, to add information to the limited knowledge base about the views, beliefs and feelings of pregnant women concerning their involvement as research participants in trials; and about their experiences of joining perinatal trials. The following chapter will present the methods used to explore these issues among the women taking part in the Magpie Trial and its follow up study.

Chapter 3

QUOTE Study research methods

3.1 Introduction

The aim of the QUOTE (Qualitative Understanding of Trial Experience) Study was to add to the knowledge base about the beliefs and feelings of research participants concerning their involvement in trials. In order to accomplish this I explored women's views about their participation in the Magpie Trial in the UK. The study also aimed to determine the women's understanding of the purpose of the Magpie Trial and their evaluations of both written and oral information given to them at the time of recruitment. An additional aim was to provide information to researchers about how such trials are perceived by participants. Examining women's views and experiences of joining the Magpie Trial in-depth was fundamental to answering the aims of this study and it was therefore necessary to develop a research design appropriate to this. Decisions were made on the basis of which design and approach was likely to answer the research aims and questions most effectively and efficiently.

The research techniques utilised in the QUOTE Study were in part also determined by procedures already in place as part of the Magpie Trial follow up study. The first part of the QUOTE Study involved analyses of data about trial experience which were already being collected as part of the women's UK follow up study postal questionnaire (described in Chapter 1). The analyses of responses to the questions that related to trial experience are presented within this thesis. The second part of the study, which forms the main element of QUOTE, was designed to examine in-depth the women's experiences of joining the Magpie Trial. This information was gained by interviewing a subgroup of women who completed the postal questionnaire. Therefore, QUOTE is predominately a qualitative study, complemented by analyses of additional data already being collected from a postal questionnaire. The postal questionnaire generated both quantitative and qualitative data, the semi-structured interviews were entirely qualitative. The

QUOTE Study was an excellent opportunity to bring together two very different methodologies. The data generated from these two sources (questionnaires and interviews) has been integrated. This chapter will describe in detail a description of the methods together with a rationale for their use, and the study procedures undertaken.

3.2 Theoretical basis of methods used

To meet the aims of the research study it was decided that qualitative interviews would form the principal method of data collection. To provide evidence of the generalisability of these qualitative findings, additional, complementary data from postal questionnaires used in the follow up study were also made available. The combination of the methods strengthened the overall ability to meet the study's aims.

3.2.1 Mixed methods approach

The QUOTE Study, then, was conducted using both quantitative and qualitative methods. These two approaches to research tend to be portrayed as opposing; qualitative, interpretive, naturalistic or ethnographic: quantitative, natural science based, hypothetico-deductive or scientific (Robson 1993:303). This rigid demarcation of qualitative and quantitative research as opposing traditions does not encourage movement or interaction between the two camps (Barbour 1999).

A number of researchers (see, for example, Schwandt 1990:258, Guba and Lincoln 1994:17) have suggested that the two approaches are not compatible and so should not be combined, due to a fundamental conflict between the two paradigms with regard to the nature of the knowledge, the relationship between researcher and subject of inquiry, and the appropriate means of generating knowledge. However, while qualitative and quantitative traditions differ, both have a common research purpose: to achieve results that have significant implications (Murphy et al 1998:57). Combining these two approaches has been termed 'mixed methods'. It has been defined as research in which the investigator collects and analyses data, integrates the findings, and draws inferences using both qualitative and quantitative

approaches or methods in a single study or a programme of inquiry (Tashakkori and Creswell 2007).

The concept of mixing different methods most likely originated in 1959, when Campbell and Fiske used multiple methods to study validity of psychological traits. They encouraged others to use their "multimethod matrix" to examine multiple approaches to data collection in research (Campbell and Fiske 1959). Recognising that all methods have limitations, researchers felt that biases inherent in any single method could neutralise or cancel the biases of other methods (Creswell 2003). The integration of these two methods within research projects is becoming increasingly important to researchers (Barbour 1999), and some now regard the two approaches as complementary rather than competitive (Pope and Mays 1995, Hicks 1996:3, Morgan 1998, Lavender and Chapple 2003, Snowdon et al 2004:108, Bryman 2006). These researchers suggest that: many of the believed contradictions are exaggerated, the complexity and diversity of today's health care system requires new multi-paradigm approaches, both approaches emphasise scientific rigour and critical analysis; and combining the two methods may generate deeper insights than one method alone and so should be seen as an essential component to research.

In midwifery and obstetrics using both approaches has been shown to ensure that the quality of the provision of care is enhanced (Hicks 1996:3). Critical appraisal of papers reporting the results of mixed methods research found a greater depth and understanding of the issues than would have been possible using either method alone (Kinn and Curzio 2005). Bringing together these two approaches for some is seen as a distinct research approach in its own right (Bryman 2006). All methods have their strengths and weaknesses and therefore adopting a multi-method enquiry can match the strength of one to the weakness of another, and vice versa (Robson 1993:303). Each method used allows testing of one source of information against another, a process known as 'triangulation' (Webb et al 1966). This process is a means of overcoming the bias that attains to a single method. Campbell and Fiske (1959) argued: "when a hypothesis can survive the confrontation of a series

of complementary methods of testing, it contains a degree of validity unattainable by one tested within a more constricted framework of a single method".

Their complementarity is based on the strengths of one method to enhance the performance of the other. Qualitative research has good validity (Murphy et al 1998:167); however, it has been critically questioned for problems of reliability and generalisability (Kennedy 1979, Silverman 2005:6). In contrast, quantitative research has been perceived to be able to demonstrate reliability and generalisability (Pocock 1983:50), but has been criticised on the validity of its findings (Guba and Lincoln 1994:163). Combining the approaches helped to tap into the strengths of both. The ultimate aim was to develop a valid study with reliable and generalisable findings.

The rationale for the mixed-method strategy used in the QUOTE Study was driven by pragmatic reasons: I was given responsibility for analysing the data obtained from the three trial experience questions on the postal survey. The use of the mixed-methods approach allowed me to analyse statistical, quantitative results from a large sample of women and then follow up the results with a sub-group of the women, to probe further and explore those results in more depth. The data collection was both concurrent (postal questionnaires producing both quantitative and qualitative data at the same time) and sequential (postal questionnaires followed by semi-structured interviews) (Creswell 2003: 211).

The mixed-method model approach has many strengths, allowing one method of data collection to assisting the interpretation of findings from the other (Sosulski and Lawrence 2008). The sequential design used in the QUOTE Study allowed for qualitative data collection (the semi-structured interviews) to assist in explaining and interpreting the findings of the quantitative data (the postal questionnaires). Confirmation of findings derived from a small number of women with a larger group, so supporting generalisability of the findings. Using multiple methods also enabled

exploration of the extent to which different methods elicit different data (Moffatt et al 2006).

During the interpretation phase, the mixed methods strategy integrates results obtained from the two methods in an attempt to confirm, cross-validate, or corroborate findings within a single study (Johnson et al 2007). This interpretative process can either note the convergence of findings as a way to strengthen the knowledge claims of the study; or seek to explain any lack of convergence that may result (Creswell 2003: 217). Within the QUOTE Study although priority was given to the weight of evidence obtained from the qualitative data, integration occurred at both the analysis and interpretation phases of the research. Bringing together the findings provided a better understanding of the women's experiences, complementing the individual strengths of each method with no overlapping weaknesses.

3.3 Methods of data collection

3.3.1 Follow up Study questionnaires

The women's self-completion postal questionnaire was used in the Magpie Trial follow up study predominately to obtain information regarding the long-term sequelae of pre-eclampsia. The trial organisers, particularly the clinical co-ordinator, Professor Lelia Duley, felt this was a valuable opportunity to obtain additional information from the women regarding their involvement in the trial. Three questions relating to trial participation were therefore added to the questionnaire. Professor Lelia Duley devised the questions, in consultation with Professor Diana Elbourne. The nature of these additional questions and the choice of questionnaires as a method of data collection decisions were therefore already made prior to the inception of the QUOTE Study. I did not devise this section of the study. However, obtaining these additional data and analysing them as part of this thesis was viewed as extremely useful.

There are many benefits to using questionnaires as a means of data collection. Postal questionnaires are a potentially quick and cheap method of collecting great amounts of information from large numbers of people

scattered over wide geographical areas (Parahoo 2006:298). They also offer the advantage of being able to be completed in the respondents' own time and at their convenience (Bowling 2002:259). The questionnaire used in the follow up study enabled large numbers of women throughout the UK to provide information regarding the long-term sequelae of pre-eclampsia, which was particularly relevant to the Magpie Trial Follow up study; and, additionally, give their views regarding participating in the trial.

The main disadvantage of postal questionnaires is their typically low response rates. Poor response rates to postal questionnaires can introduce bias and reduce the statistical power of the study (Brealey et al 2007). Although these can be increased, for example, by the use of follow up mailings and incentives (Edwards et al 2007). There is inconsistency in the literature as to what constitutes a sufficient response rate. Robinson (1989) recommends 65% as an acceptable rate; others recommended the rate of 75% as the minimum acceptable standard (Fowler 1993:40). The response rate to the Magpie Trial follow up postal questionnaire was 81% (n=619).

Another important limitation of postal questionnaires, (as with all research methods), is that respondents may differ significantly from non-respondents (McColl et al 2001:21). Oppenheim (1992:106) encourages the researcher to ensure that non-responders have the same attitudes or experiences as responders to survey questionnaires, and to try and ensure that the reasons for their non-response are purely situational or at any rate not connected with the topic of the survey. The data gathered from the Magpie Trial on women at trial entry could be compared with respect to a number of characteristics including maternal age, gestation, severity of pre-eclampsia and eclampsia. Therefore any important differences in these factors between the women who responded and those who did not could be identified and explored.

Based on the research literature about questionnaire response (Edwards et al 2007), the Magpie Trial co-ordinators gave a great deal of consideration to the overall appearance of the postal questionnaire. Attention was given to the layout, including its length (3 sides of A4, see Appendix 5 for full

questionnaire), and ease of answering. Each questionnaire was personalised. The order of questions followed a logical sequence, and questions were grouped by topic. The three questions relating to trial participation came at the end of the questionnaire (questions 14, 15, and 16), and involved a mixture of open and closed responses (see Appendix 8). For ease of reading this thesis the questions have been re-numbered (1, 2, and 3).

The first of the three questions relating to trial experience, asked the women whether they would agree to participate in the Magpie Trial again. This question used a five point rating scale, with a middle response category. This response options were: definitely yes, probably yes, not sure, probably no, definitely no. The questionnaire included space for additional free text, where women were invited to explain their choice of fixed response.

The second and third questions asked the women to record in their own words anything that could have been done to improve their experience of joining (Q2) and anything that was particularly good about joining the trial (Q3).

Included with each questionnaire was a cover letter (Appendix 2) reminding the women about their participation in the Magpie Trial and offering help with completion of the questionnaire. A pre-paid envelope was also provided. Reminders were sent after one month. If there was no response, a second reminder was sent by recorded delivery, or the women were contacted by telephone.

3.3.2 QUOTE Study semi-structured interviews

The interview is a flexible and adaptable way of finding things out. It has been acknowledged that the interview is a kind of conversation: a conversation with a purpose (Maykut and Morehouse 2004:33, Robson 1993:227). According to Cohen et al (2007:56) it is one 'initiated by the interviewer for the specific purpose of obtaining research-relevant information and focused by him *(sic)* on content specified by research objectives of

systematic description, prediction or explanation'. Much qualitative work is interview based, and it has been suggested by Britten (1995) that there are three main types of interviews: structured, semi-structured and in-depth interviews.

Structured interviews consist of administering structured questionnaires, with interviewers trained to ask questions (mostly fixed choice) in a standardised manner. It has similarities to the quantitative survey and is predominately utilised in this way (Walsh and Baker 2004:63). The classic market survey commonly involves this approach. Structured interviews do not exclude the possibility of the use of unstructured questions but these are the prerogative of the interviewer, not the interviewee.

Semi-structured interviews are based on a loose outline of open-ended questions centred on a single topic. This format allows the interviewer and interviewee some flexibility to diverge from the outline and add to or develop questions. In-depth interviews allow the researcher to focus in considerable detail on one or two issues. Both types of interview require sensitivity and flexibility from the interviewer, and the careful use of follow up questions or 'probes' to draw out the topic and gather really detailed information. One of the strengths of semi/unstructured questions is their potential for uncovering unanticipated ideas or aspects of the research question not previously considered (Pope and Campbell 2001). The semi-structured interview provides the interviewer with an opportunity to follow up interesting responses and observe non-verbal cues which may give messages which help to understand the verbal response, possibly changing or in some cases reversing its meaning, which in turn gives the potential for providing rich and illuminating material. It is important to acknowledge, however, a limitation to this method is that people may find being interviewed and talking about their experiences a difficult process (Robson 1993:227).

Semi-structured interviews were considered the most appropriate form of interview when considering the objectives of this study. This style of interview allowed similar topics to be covered with each of the women, while still

allowing the women to have flexibility in their answers and identify areas perhaps neglected by the interviewer. It allowed the pre-specified topics to be discussed and explored in detail, as well as new areas or ideas to be uncovered. Such interviews also allow the interviewer to check that they have understood the respondent's meanings, instead of relying on their own assumptions (Britten et al 1995). This was particularly important in the QUOTE Study, as there could be potential for misunderstanding if the women were unfamiliar with methodological terminology such as randomisation, placebo and equipoise. It could not be assumed that the women used methodological terminology in the same way as myself. The interview allows for questions not to be standardised; therefore the interviewer can use the interviewee's own vocabulary when framing questions.

Preparation for interviewing can be very time consuming. Arrangements to visit, securing necessary permissions, confirming arrangements, rescheduling appointments if necessary all require plenty of time. The transcribing of the tapes from semi-structured interviews is an immensely time consuming process also; according to Britten and colleagues (1995), one hour of interview can take six or seven hours to transcribe. The actual interview session itself can vary in length depending on the areas being addressed. For some anything under half an hour is unlikely to be valuable; anything going much over an hour may be making unreasonable demands on busy interviewees, and could have the effect of reducing the number of persons willing to participate, which may in turn lead to biases in the sample (Robson 1993:227). The interviews carried out for the QUOTE Study lasted between 35 and 120 minutes. The women themselves dictated the length of the individual interviews, by either giving short or lengthy responses to the questions.

A specific problem for this study was having all the interviews performed by myself (research midwife for Magpie Trial). It was acknowledged by the research team that this might make it difficult for some women to talk openly about their experiences of joining the trial, especially if they had a negative experience. In order to minimise this effect and verify the extent of the

problem, another interviewer (LW), who had no previous involvement with the Magpie Trial or the QUOTE Study was enlisted to perform some (n=10) of the interviews. This interviewer was a midwife and aware of the aims and procedures of the Magpie Trial and its follow up study. I provided her with additional detailed information; including The Magpie Trial protocol and results, and the follow up study protocol. Comprehensive information was also supplied about the QUOTE Study including its protocol and interview schedule. I ensured LW was familiar with all study procedures prior to the interviews. Periodically we met and read over each other's interview transcripts and discussed similarities and differences. At the point of interview both interviewers, but not all women, were blind to treatment allocation. The women had been previously informed they could request information regarding their treatment allocation by writing to the trial co-ordinating centre, three of the women interviewed had done this and were aware of their treatment allocation.

During the time the follow up study was in progress the main Magpie Trial results were published (Magpie Trial Collaborative Group 2002). As a consequence of publishing the trial results there was much media coverage (television and newspaper interviews with the principal investigator and members of the trial management team) and soon after a lay summary was posted to all women (Appendix 6). In practice this meant the women interviewed were aware of the trial results.

The interview schedule was designed to address four broad topic areas:

- Understanding of the Magpie Trial, including its aims and methodology;
- Experience of being recruited and views of trial information received;
- Thoughts since joining the trial, including about receiving results and being involved in the follow up study;
- Views on perinatal research generally.

The interview schedule (Appendix 9) was informed by previous published research within this area, my own experience of working on research trials,

and expert opinion. The use of an interview schedule ensured consistency and that all the women were asked about the same topics. There was flexibility in wording and in the order and presentation of the topics; however; this did not change the agenda or purpose of the interviews. By allowing some freedom of the interview schedule the aim was to help the women to explore and discuss their experiences more easily.

The focus of the interview was exploring the women's *perceptions* of their experiences. I did not 'test' how much the women had *actually* understood, the focus being on participation of the Magpie Trial from the point of view of the women.

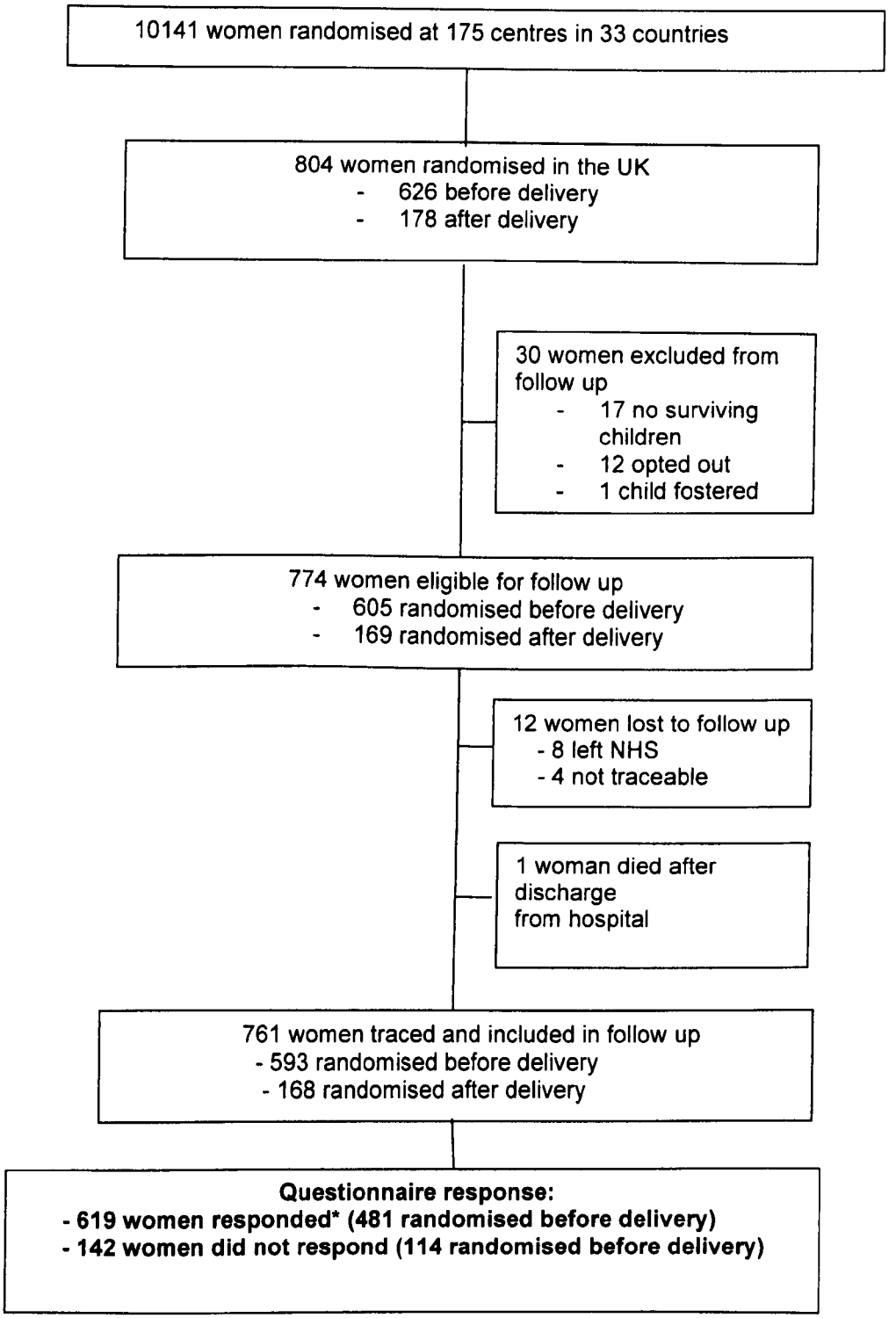
3.4 Sample of research participants

3.4.1 The postal questionnaire

Between July 1998 and November 2001, 804 women were recruited to the Magpie Trial across 67 UK hospitals. Follow up was done from October 2002 until May 2004. Seventeen women with no surviving child at discharge from hospital were excluded from contact, as were 12 women who opted out of follow up, and one woman whose child was fostered. In total 774 women were eligible to be contacted for Magpie Trial follow up. In order to contact the women, they needed to be traced. This process confirmed eight women had left the NHS and could not be traced further and an additional four were not traceable. No women died before discharge from hospital, three died after discharge; one prior to the postal questionnaire being sent, two after postal questionnaires were sent. The causes of death were stroke; asthma; and non-Hodgkins lymphoma. A response was received from 81% (619/761) of the eligible women. It was necessary for reminder letters to be sent and telephone calls to be made to some (54%), and for 59 women the questionnaire was completed over the phone. The response rate makes this study larger than most previous studies pertaining to trial experience.

Although the Magpie follow up study aimed at assessing children at two years of age (corrected for gestation at birth), this was not always realised, as follow up of the earliest recruited children did not commence until the main

Magpie Trial was complete. Hence the interval between randomisation and questionnaire completion was greater for those women and children recruited early in the trial. Questionnaires were completed on average 24 months (median, inter quartile range 23-31 months) after the child was born. Evidence of representativeness and generalisability of the results obtained, rests on two factors: the high response rate (81%), and that women were recruited UK wide. The flow chart of the women who were ultimately eligible for receipt of a questionnaire is shown in Figure 3.1.



* Includes 2 women who died after completing their questionnaire

Figure 3.1 Women eligible for postal questionnaire

Characteristics of women responding (n=619) and those not responding (n=142) to the postal questionnaire were compared, using data gathered at

entry to the Magpie Trial. Characteristics at trial entry and outcome at discharge from hospital were similar for both groups of women (Table 5.1). The exception was for women who were aged <20 years at trial entry. A higher proportion of those who did not complete a questionnaire were aged <20 years compared with those that did (19% versus 8% relative risk (RR) 0.36, Confidence Interval (CI) 0.21 to 0.60). More women who delivered by caesarean section or received trial treatment for longer than 12 hours returned their questionnaire: 61% versus 55% (RR 1.27, CI 0.84 to 1.91) and 84% versus 77% (RR 1.53, CI 0.98 to 2.39) respectively.

Of women who responded to the questionnaire, three quarters (73%) were primiparous, over two thirds (61%) were delivered by caesarean section and less than a quarter (22%) had delivered before trial entry. The average age of the women was 29 years (mean, SD ±6.078). For the children, many were at high risk for prematurity. For example over a third of births were ≤34 weeks gestation at trial entry, (35.05 weeks mean, SD± 3.708).

	Responders		Non-responders*	
	n= 619	(81%)	n = 142	(19%)
Characteristics of women				
Primiparous	453	(73%)	99	(70%)
Multiple pregnancy	29	(5%)	5	(4%)
Age (less than 20 years)**	48	(8%)	27	(19%)
Severe pre-eclampsia	284	(46%)	66	(46%)
Imminent eclampsia	166	(27%)	39	(27%)
Delivered before trial entry	138	(22%)	28	(20%)
Randomised magnesium sulphate	303	(50%)	74	(52%)
Outcome after randomisation – maternal				
Eclampsia	4	(<1%)	2	(1.4%)
Admission to high dependency care	521	(84%)	122	(86%)
Admission to intensive care	6	(<1%)	1	(<1%)
On trial treatment more than 12 hours	517	(84%)	109	(77%)
Side effects	112	(18%)	32	(23%)
Randomised before delivery	477		114	
Caesarean section	291	(61%)	63	(55%)
Induction of labour	271	(57%)	64	(56%)
Outcome – Infant				
≤34 weeks at delivery	190	(40%)	31	(27%)
≤34 weeks at trial recruitment	163	(34%)	33	(29%)
Admitted to neonatal unit	325	(68%)	65	(57%)

*Non-responders: women in receipt of questionnaire but did not complete and return

** statistically significant when comparing those responding and those not

Table 3.1 Characteristics at trial entry of women who responded and those who did not

3.4.2 Semi-structured interviews

Purposive sampling:

Cluette and Bluff (2006:183) define theoretical sampling as 'sampling that is determined by concepts, categories and emerging theory that is grounded in the data'. In order to ensure that meaningful exploration could be made between different women's experiences of the Magpie Trial a form of

theoretical sampling involving specification of a purposeful sampling matrix (Kuzel 1986) was used. The matrix was devised to aid recruitment. It was acknowledged that the women's experiences, perceptions or recall of the Magpie Trial could be influenced by a number of factors. In specifying the matrix, it was important to explore which characteristics were likely to impact on women's perceptions; and in order to do this discussion took place between the members of the study team (RS, AJ, DE). Initially, team members identified a large number of characteristics, some with clearly identifiable links to women's perceptions, others not so easily definable, which it was hypothesised could be associated with the women's perceptions of the Magpie Trial. Including too many characteristics would make the matrix too complex, unmanageable and therefore ineffective. The final sampling matrix was therefore based on a pragmatic approach and includes only a few characteristics that were considered the most important. However, in order not to discount the potential effects of the other identified characteristics, they were explored in relation to the questionnaire responses, and are described fully below (section 3.5 Analysing the data).

Those that were identified as important for inclusion in the matrix were: whether the resultant child had some degree of developmental delay or the woman herself was suffering long-term hypertensive problems; as it was thought possible that such women could attribute their problems to the trial and therefore view the study in a negative way; and pregnancy status at the time of recruitment, since approximately 78% of the women were recruited to the Magpie Trial while still pregnant this too could potentially influence their perceptions of the trial, given that the difficulty parents face when asked to consent to a research trial in which an unborn baby's needs are to be considered.

Thus the pre-specified characteristics in the final sampling matrix for the interviews were:

- Possibility that the resultant child, irrespective of timing of randomisation, had some degree of development delay (ASQ screen positive),
- The woman herself having persistent hypertension since joining the Magpie Trial (poor outcome),
- Being recruited to the Magpie Trial while still pregnant.

A sub-sample of women who returned their completed questionnaires were eligible for interview. For practical reasons women were defined as eligible if they lived within a 100 mile radius of Liverpool (I was based there). Recruitment was therefore confined to six maternity units within this geographical area. The six units were located in four counties (Cheshire, Merseyside, Staffordshire and Yorkshire), and were a mixture of district general and teaching hospitals. In total 219 women were recruited to the Magpie Trial from these hospitals, among whom a 83% (n = 181) response rate to the follow up study postal questionnaire was achieved. Forty-five of these 181 women were offered a Magpie follow up study home visit as their children screened positive and required further assessment (Bayley assessment) in order to confirm or exclude developmental delay. These women were therefore eligible to be interviewed for QUOTE. Of the remaining families whose children screened negative, 30 were potentially eligible (see Figure 3.2).

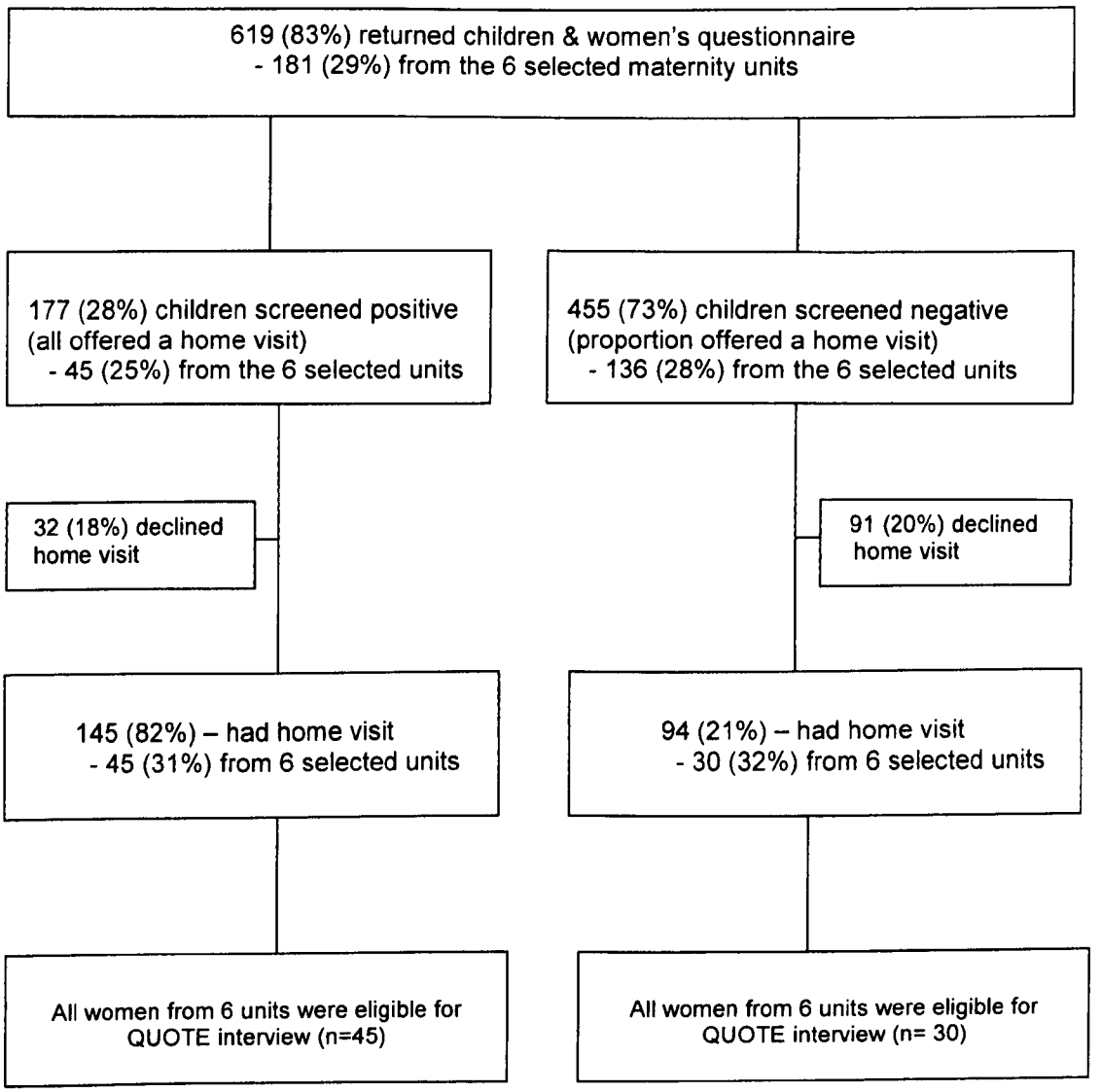


Figure 3.2 Women eligible for QUOTE Study interview

I purposefully identified individual women in order to include the key QUOTE sampling matrix characteristics. Women were then selected and invited for interview. At the beginning of the study it was impossible to estimate the number of women who would fall into each of the sampling matrix. The numbers of individual interviewees in qualitative studies is usually much smaller than in quantitative survey research (Pope and Campbell 2001). A sample size generally regarded as 20-50 would appear adequate (Holloway and Wheeler 1996:128, Kuzel 1999:33, Patton 2002:242). The essence of qualitative research is to provide explanations and understandings of what is happening through in-depth examination, rather than to provide a statistically representative picture (Pope and Campbell 2001). Recruitment to each of the pre-specified groups was stopped when there was little extra data gained

from the latest interview (data saturation). Therefore the length of time it took to recruit sufficient numbers into any given group varied. All women who agreed were interviewed, even if data saturation was achieved.

I continuously examined the characteristics of interviewed women, in order to assess whether the intended range of women was being sampled. It became apparent that, initially, few women who themselves had a poor outcome were being offered an interview. Therefore, I purposefully invited more of these women for interview. Within the pre-specified geographical area nine women met this criterion, all of whom were sent a postal invitation. Of these, four women did not respond to the initial postal invitation and therefore were not contacted again and the remaining four women were interviewed.

It can be seen from the sampling matrix (Table 3.2) there were no women eligible to be interviewed whose children screened negative on the ASQ and who had themselves had a poor outcome. Thirty-three women were identified as having a poor outcome in the overall UK sample; four belonging to the six pre-specified units. The final number of 40 completed interviews appeared sufficient to cover a wide variation of characteristics and was adequate to offer depth and richness in the range of views, understandings and experiences in this population. Detailed summaries of the women's characteristics are given in Appendix 10.

ASQ Scored Positive Children (24)				ASQ Scored Negative Children (16)			
Women Poor Outcome (4)		Women Good Outcome (20)		Women Poor Outcome (0)		Women Good Outcome (16)	
Antenatal Recruit (2)	Postnatal Recruit (2)	Antenatal Recruit (17)	Postnatal Recruit (3)	Antenatal Recruit (0)	Postnatal Recruit (0)	Antenatal Recruit* (13)	Postnatal Recruit** (3)
Home visit (2)	Home visit (2)	Home visit (17)	Home visit (3)	Home visit (0)	Home visit (0)	Home visit (4)	Home visit (2)

*No home visit n=9, ** No home visit n=1

Table 3.2 sampling matrix

Recruitment:

Methods of recruitment for the QUOTE Study interview depended on whether the women had had a home visit or not.

Home visit performed:

At the end of the home visit eligible women (those from the 6 pre-selected units) were invited to take part in the semi-structured interview at a later date. If they were willing, in principle, to consider participation they were given the QUOTE Study information leaflet, consent form and prepaid envelope (Appendices 11 and 12). As I had performed the majority of the home visits and would be carrying out the majority of the qualitative interviews the women were not required to decide either to join or decline participation to the interview at the home visit. Rather, women were asked to consider having an interview and, if agreeable, sign the form and return it in the prepaid envelope in their own time to the trial co-ordinating centre.

Home visit not performed:

After receipt of the completed children's and women's questionnaires a random sample (n=16) of women not eligible for a home visit (child screened negative on ASQ) were sent a letter informing them about the QUOTE Study

and inviting them to take part in a semi-structured interview (Appendix 13). The Magpie Trial co-ordinating centre identified these women. The women were required to actively opt into the study by considering and signing the consent form and returning it in the prepaid envelope in their own time. My contact number was on the information leaflet should they have needed to discuss the study further.

One written reminder was sent two weeks after the home visit had been performed or letter of invitation sent (if no home visit), to those women that had not returned the signed consent form. If no reply had been received within a month it was assumed the woman did not want to take part in the QUOTE Study and no further contact was made. Therefore timing of the interview was dependant on when the women returned the signed consent form. As soon as written consent was obtained women were contacted to arrange a time for the interview. The interview took place at the woman's home. All women were sent a thank you letter after the interview acknowledging their involvement in the study (Appendix 14).

3.5 Analysing the data

3.5.1 Quantitative data analysis for the questionnaire responses:

To ensure that meaningful exploration could be made of the women's fixed responses, they were compared in relation to a number of pre-specified characteristics of the women and of events around their delivery for which information was collected at the time of entry to the Magpie Trial (as previously discussed). In specifying characteristics likely to be relevant to the analysis, consideration was given to those thought likely to have an impact on women's perceptions of their experience of the trial. Factors were pre-specified as primary and secondary characteristics for the analysis. Primary characteristics were whether the woman had been randomised magnesium sulphate or placebo, and whether she had reported side effects from trial treatment, and whether. These two characteristics are related, as women who received magnesium sulphate were more likely to have had side effects than those who received placebo (Magpie Trial Collaborative Group 2002).

Primary characteristics were:

(i) Allocated group at trial entry (magnesium sulphate or placebo)

(ii) Experience of side effects or not while on trial treatment

Secondary characteristics were:

(iii) Age at recruitment (less than 20 years)

(iv) Woman's occupation

(v) Women's level of education

(vi) Parity - primiparous or multiparous

(vii) Recruitment to the Magpie Trial while still pregnant or delivered

(viii) Single or multiple pregnancy

(ix) Severity of pre-eclampsia

(x) Having had an eclamptic fit

(xi) Length of time on trial treatment (more than 12 hours or less)

(xii) Delivered by caesarean section

(xiii) Child born prematurely (<34 weeks gestation or more)

(xiv) Child admitted to neonatal intensive care unit (NICU)

(xv) Timing of response to follow up study questionnaires (>2 weeks or less)

(xvi) Possibility of development delay in the child (ASQ screen positive)

(xvii) Poor maternal outcome (renal problems, stroke, severe hypertension, any chronic illness since birth of baby)

(xviii) Declined or agreed to a follow up home visit

(xix) Postnatal depression reported by the woman or general practitioner

The computer software Statistical Package for the Social Sciences (SPSS) was used to analyse the data, which for the sake of accuracy was double entered. Descriptive statistics in the form of frequency counts were computed. Question 1 generated numerical data for a pre-specified tick response dependent variable with five categories (definitely yes, probably yes, not sure, probably no, definitely no). The data were treated as an ordered categorical variable, and the non-parametric test used was the chi-squared for trend test. The Chi squared test was used for the analysis of the

association between the characteristics. Prior to running the analysis, primary and secondary characteristics were pre-specified.

For the primary characteristics, statistical significance was taken as p value of <0.05, and for secondary characteristics as <0.01. The null hypothesis tested was 'There is no difference in the distribution of frequencies across categories between the groups'.

3.5.2 Qualitative data analysis from the postal questionnaires:

Women were asked, as part of Question 1, to explain why they had chosen a particular fixed response category (i.e. definitely yes, probably yes, not sure, probably no, or definitely no). For this analysis the free text verbatim answers were grouped according to the fixed response category they came from, thus allowing investigation of their explanations within the context of their chosen category.

3.5.3 Qualitative data analysis for the semi-structured interviews

Analysis of the data began prior to completion of data collection, an approach recognised and encouraged by Miles and Huberman (1994:56). The first stage began with transcribing the tape-recorded interviews. I then read the transcripts over many times in order to gain an overall impression of the data. This repetitive process often revealed potential codes. Sandelowski (1995) expresses this process as the breaking up or down of the data to permit the researcher to see it in a new way. The next stage of analysis was by done by performing formal line-by-line analysis as described by Morse and Field (1996:101). The following stage was to develop an index for the content (Polit and Beck 2006:399). This involved creating a coding scheme, with the support of a qualitative computer analysis package (WinMax pro) to facilitate the analysis. This stage of the analysis related to the major points of interest and shared characteristics. After coding the data it was necessary to identify and select patterns and themes. The data were then grouped together within the defined themes.

In some qualitative studies, the findings are returned to the participants in order to provide evidence of their validation, a process referred to as 'member checking' (Carter 2004:93). This includes techniques in which the interview transcripts are either returned to the participants so that they can add, delete or clarify issues or the researcher's account is compared with those of the participants, to establish a level of agreement between the two sets. Such an approach is, however, controversial as a genuine test of validity, Meadows and Morse (2001:197) maintain that ensuring credibility is the responsibility of the research team. Others argue that accounts produced by researchers are designed for a wide audience and will, inevitably, be different from the accounts of an individual participant simply because of their different roles in the research process (Mays and Pope 2000). Member checking therefore was not used in the QUOTE Study.

However, so as to minimise possible interpreter bias and assess the plausibility and trustworthiness of my interpretation of the data, a sample of the interviews were themed independently by the other members of the study team (AJ and DE). In reporting the findings, it was considered important to provide sufficient amounts of data (excerpts of the interview transcripts) to allow any reader to identify the foundations upon which the conclusions of the study have been grounded. This process of transparency described by Popay et al (1998) allows a critical scrutiny of the researcher's interpretation of the data and further evaluation of the robustness of the findings. (Samples of additional supporting quotes from the women are provided in Appendix 18).

3.6 Ethics approval, consent and confidentiality

3.6.1 Approval

Research ethics approval for the Magpie Trial follow up study, which included the postal questionnaire, was gained as an amendment to the original trial protocol of the main Magpie Trial. Approval for the QUOTE Study interviews was obtained from the NorthWest Multi-Centre Research Ethics Committee (MREC) (see Appendix 15 for approval). Local Ethics Committee approval was not required.

3.6.2 Consent

As described earlier, all women eligible for follow up were given the opportunity to opt-out. Those agreeing to remain in the follow up study were sent a postal questionnaire to complete. Reminders were sent to encourage women to respond, but otherwise it was the decision of the women themselves as to whether they completed the questionnaire. If a woman did not respond after two written reminders no further contact was made with the woman.

Women were invited for the QUOTE interview by being given an information leaflet explaining the purpose of the study, They were required to actively opt into the study by returning their signed consent form in a pre paid envelop in their own time, thus again avoiding any pressure from the research team.

3.6.3 Confidentiality

Initially the questionnaires were identified to the particular woman to ensure reminder letters were sent appropriately by the trial co-ordinators. After this process was complete each questionnaire was assigned a code to secure the woman's anonymity. In the analysis and reporting stages I, as the primary researcher was the only member of the research team to have access to this information. The data from the interviews and questionnaires were transcribed as soon as was possible.

3.6.4 Handling and Storage of Data

The Magpie Trial data manager in Oxford administered all the postal questionnaires. Data from the questionnaires were input onto the trial computer system at the University of Oxford. This data were kept on the computer and secured by password. Disks and paper data were kept in a locked cupboard. All data from the interviews were held in the University of Liverpool using the same procedures.

3.7 Conclusion

As described the study was conducted in two distinct parts. All UK women remaining part of the follow up study (n=761) were sent a postal

questionnaire, which included questions relating to their participation in the Magpie Trial. Following completion of this questionnaire, a sub-set of these women were offered a semi-structured interview to find out, in more detail than was possible in the questionnaire, about their experiences of joining the trial. The analyses of the data obtained are now detailed in the following five chapters. Chapter 4 presents the findings from the three questions included in the postal questionnaire and chapters 5 - 8 from the semi-structured interviews.

Chapter 4

Findings from the postal questionnaire

4.1 Introduction

This chapter provides a detailed presentation of the findings from the Magpie Trial follow up study postal questionnaires. The main focus of the questionnaire was to assess the women's health, and any contact they had with the health services in the period between trial recruitment and follow up. An additional section in the questionnaire comprised three questions relating to experience of participating in the Magpie Trial. The first part of this chapter presents the quantitative findings relating to the first of the three questions; this question also produced qualitative data, which are also presented. Questions 2 and 3 produced solely qualitative data.

During the time the follow up study was in progress, the main Magpie Trial results were published (Magpie Trial Collaborative Group 2002), and soon after a lay summary was posted to all women (Appendix 6). As a consequence of publishing the trial results there was much media coverage (television and newspaper interviews with the principal investigator and members of the trial management team). In practice this meant some women heard the coverage and received a written summary of the results before receiving the postal questionnaire, for others the questionnaire reached them afterwards.

4.2 Responses to question 1

Overall, 619 (81%) women completed a postal questionnaire, and 99% answered question 1. This question asked, ' If time suddenly went backwards and you had to do it all over again, would you agree to participate in the Magpie Trial?' and used fixed response options, together with space for additional free text, where women were invited to explain their choice of response.

The fixed response options the women were provided with were:

- Definitely yes
- Probably yes
- Not sure
- Probably no
- Definitely no

Overall, most women (85%) had a positive attitude towards the Magpie Trial, confirming that they would agree to participate in the trial again - although only just over half (58%) said they would definitely participate again, and just over a quarter (27%) probably would (Table 6.1).

Fixed response categories to postal questionnaire 619 (81%)		
Definitely yes	356	(58%)
Probably yes	169	(27%)
Not sure	34	(5%)
Probably no	23	(4%)
Definitely no	33	(5%)
Not answered	4	(1%)

Table 4.1 Fixed response categories

Pre-specified characteristics

The response categories (definitely yes, probably yes, not sure, probably no, definitely no) chosen by the women were examined further in relation to the associations with the pre-specified characteristics (for list of characteristics see Chapter 3)

4.2.1 Fixed responses compared to pre-specified characteristics *(see Table 4.2)*:

(i) Randomised to magnesium sulphate ($MgSO_4$):

Of the 302 women randomised to receive magnesium sulphate, 85% said they would agree to join the Magpie Trial again. There was no evidence of a relationship between women's responses to question 1 and randomised group (Table 4.2; x^2 =1.06, p= 0.302).

(ii) Side effects:

In all, 112 (18%) women were reported to have experienced side effects from their treatment. These women were statistically significantly more likely to respond unfavourably (probably would not join if asked again) (14% experiencing side effects compared with 1% not), (Table 4.2; x^2 =6.62, p= 0.010).

Fixed responses compared to primary characteristics†												
	Def yes		Prob yes		Not sure		Prob no		Def no		Total	P-value
Primary characteristics												
Randomised $MgSO_4$	165	55%	92	30%	12	4%	19	6%	14	5%	302	0.302
Randomised placebo	191	61%	77	25%	22	7%	4	1%	19	6%	313	
Side effects	53	47%	35	31%	4	4%	16	14%	4	4%	112	0.010*
No side effects	290	60%	125	26%	29	6%	7	1%	28	6%	479	
Not known	13	5%	9	37%	1	4%	0	0%	1	4%	24	

†4 women did not answer the question

*Statistically significant (p-value <0.05)

Table 4.2 Fixed responses compared to primary characteristics

The following table (Table 4.3) provides the responses to question 1 by range of the pre-specified secondary characteristics:

Fixed responses compared to secondary characteristics†														
Secondary characteristics	Def yes		Prob yes		Not sure		Prob no		Def no		Total	P-value
< 20 yrs at recruitment	24	50%	18	37%	2	4%	1	2%	3	6%	48	0.697
≥ 20 yrs	332	59%	151	27%	32	6%	22	4%	30	5%	567	
Professional/Managerial	96	64%	32	21%	10	7%	6	4%	6	4%	150	0.308
Skilled trade/ other	235	56%	124	30%	20	5%	14	3%	25	6%	418	
Education up to 16 yrs	119	59%	52	26%	12	6%	9	4%	10	5%	202	0.695
Beyond 16 yrs	183	60%	81	26%	17	6%	10	3%	15	5%	306	
Primiparous	262	58%	121	27%	24	5%	22	5%	24	5%	453	0.481
Multiparous	94	58%	48	30%	10	6%	1	<1%	9	6%	162	
Recruited antenatally	266	56%	137	29%	28	6%	19	4%	27	6%	477	0.104
Recruited postnatally	90	65%	32	23%	6	4%	4	3%	6	4%	138	
Multiple pregnancy	18	62%	7	24%	2	7%	1	3%	1	3%	29	0.642
Singleton pregnancy	338	58%	162	28%	32	5%	22	4%	32	5%	586	
Severe pre-eclampsia	175	61%	79	28%	9	3%	7	3%	12	5%	284	0.015
Not severe	181	54%	90	27%	25	8%	15	5%	20	6%	331	
Eclampsia	3	75%	1	25%	0	0%	0	0%	0	0%	4	0.394
No convulsion	353	57%	168	27%	34	5%	23	4%	33	5%	611	
≤12 hrs trial treatment	35	38%	20	27%	3	4%	11	15%	4	5%	73	0.009*
>12 hrs trial treatment	307	60%	140	27%	30	6%	13	2%	27	5%	517	
Not started / no data	13	54%	9	37%	1	4%	0	0%	1	4%	24	
Caesarean section	255	62%	106	26%	16	4%	12	3%	19	5%	408	0.001*
Vaginal delivery	101	49%	63	30%	18	9%	11	5%	14	7%	207	
<34 wks gestation	128	67%	41	22%	8	4%	4	2%	9	5%	190	0.015
≥34 wks gestation	229	54%	128	30%	26	6%	19	4%	24	6%	426	
Admitted to NICU	198	61%	85	26%	14	4%	9	3%	19	6%	325	0.251
Not admitted	158	54%	84	29%	20	7%	14	5%	14	5%	290	
>2 wks to return q's	225	57%	106	27%	28	7%	12	3%	21	5%	392	0.792
≤2 wks to return q's	120	59%	57	28%	5	2%	10	5%	11	5%	203	
ASQ positive	87	56%	36	23%	12	8%	6	4%	13	8%	154	0.098
ASQ negative	251	58%	127	29%	21	5%	16	4%	19	4%	434	
No ASQ	18	57%	6	22%	1	4%	1	4%	1	4%	27	
Mat outcome poor	37	58%	6	25%	3	5%	4	6%	4	6%	64	0.584
Good outcome	305	58%	148	28%	30	6%	17	3%	28	5%	528	
Do not know	14	61%	5	22%	1	4%	2	9%	1	4%	23	
Declined home visit	30	34%	33	37%	11	12%	8	9%	7	8%	89	0.0001*
Agreed home visit	313	62%	132	26%	22	4%	14	3%	25	5%	506	
Postnatal depression	9	56%	4	25%	1	6%	1	6%	1	6%	16	0.719
None	343	58%	163	27%	33	6%	22	4%	32	5%	593	
Do not know	4	67%	2	33%	0	0%	0	0%	0	0%	6	

†4 women did not answer the question

* statistically significant (p-value <0.01)

Table 4.3 Fixed responses compared to secondary characteristics

4.2.2 Analysis of verbatim text from question 1

Women were asked, as part of question 1, to explain why they had chosen a particular fixed response category (i.e. definitely yes, probably yes, not sure, probably no, or definitely no). For this analysis, the free text verbatim answers were grouped according to the fixed response category they came from, thus allowing investigation of their explanations within the context of their chosen category. As many women gave answers that were judged to illustrate a number of identified themes, the number of comments displayed in the following tables are not linked directly to the numbers of women that responded (the same applies to the women's responses to questions 2 and 3).

It was evident from the women's explanations that the Magpie Trial was not experienced or recalled in isolation but, not surprisingly, had become very much entwined in their memories of their birth experience as a whole, and at times a number of themes were evident in the one response. Women experiencing severe pre-eclampsia (and therefore eligible for the Magpie Trial) would have received high dependency care, as previously discussed. This would usually consist of bed rest; restriction of oral fluids, close clinical monitoring (blood pressure checked every 15-30 minutes, tendon reflexes checked hourly, and urine measured hourly), insertion of urinary catheter and intravenous infusion (drip) and the baby may be delivered early. Care attributable solely by the women to the Magpie Trial was an extra intravenous line and frequent unobtrusive observation of respiratory rate. However, many of the women appeared to experience difficulty in separating out what was happening to them as a direct consequence of joining the Magpie Trial and what was linked to the facts of their pregnancy and to having pre-eclampsia. This was most evident for those women who were dissatisfied with some aspect of their trial experience. These women often interpreted aspects of the nursing procedures (bed rest, drip, restriction of oral fluids) and monitoring (checking of blood pressure, tendon reflexes) of their pre-eclampsia as being connected to the Magpie Trial itself. This resulted in them often interpreting the trial in a negative way and not appreciating that irrespective of joining the trial, they would have had these procedures carried out.

Definitely yes:

Of the 356 (58%) women who chose this option, 304 (85%) gave an explanation of their response in the free text section. Women expressed benefit to themselves, benefit to others and the importance of research into pre-eclampsia as the principal reasons for participating in the trial again. The following responses (Table 4.4) illustrate these themes:

Theme	Comments (n)	Sample of women's comments
Benefit to self	112	*"Because it helped me not to get eclampsia and I've had no side effects"* *"Definitely yes, as I think that it definitely saved my life and my child's"* *"I was very ill, and think without it me and my child would have died"*
Research important	109	*"It is important that these trials continue to provide research and results in the future"* *"I'm in favour of any new research to benefit future sufferers of pre-eclampsia"* *"I feel it is very important to make a contribution to research which may help other women in the future"*
Benefit to others	107	*"Because I hope to make a difference, if by me participating in this trial helped just one woman not to go through what I did, it would make a difference"* *"Being part of the trial has not been difficult and if other women can benefit from my experience then it will have been useful"* *"If my experience can help future women, I'm glad to have participated"*
No inconvenience	40	*"The trial was of no inconvenience to me as I was on high dependency anyhow"* *"The trial was painless, not particularly awkward for me as I had to stay in hospital anyway, so I feel that if anything can be done to help learn about this condition and possibly help it should be supported"*
Led to better care	10	*"Excellent care during hospital, good follow up after discharge and having a feeling someone cares"* *"Very good care and information was available. I also appreciated the quality of the follow up and the thank you cards"* *"Got better monitoring by being in the study"*

Table 4.4 Explanation of women answering 'definitely yes'

Probably yes:

Of the 169 (27%) women who chose this option 125 (74%) gave an explanation in the free text section as to why. Comparing these women's responses with those of women who chose 'definitely yes' it was evident that although generally similar, that they had a less rewarding experience. The additional themes that emerged related to the women's understanding of what would be considered usual nursing care for pre-eclampsia and what

additional treatment and monitoring a woman would receive as part of the Magpie Trial. Some women presumed much of the nursing care they received was attributable to the trial, even though this was not the case. Some women described experiencing unpleasant side effects (in the Magpie Trial overall, 25% of women randomised magnesium sulphate experienced side effects, as did 5% of those receiving a placebo). For others it appeared they were generally less satisfied by their overall birthing experience, which was probably not attributable to the trial itself. Some women provided explanations as to why they chose this category (probably yes) and not 'definitely yes'. The explanations overleaf (Table 4.5) illustrate these themes:

Theme	Comments (n)	Sample of women's comments
Mixing clinical care with trial	18	*"Only reservation was that I did not know what was required of me i.e. the taking of my reflexes throughout the night of the birth and that any sleep did not seem an option. Also this monitoring seemed in some instances questionable"* *"During administration I was uncomfortable – couldn't rest since I had to be monitored half hourly and thereafter for about 24 hours"* *"I hated every minute because I was quite uncomfortable as I was stuck in bed in the labour room for more than 24 hours because I had to stay there they wouldn't let me on the ward with the trial. Also the drip part hurt my hand, it also made positions difficult"* *"When I was in HDU, I seemed to have so many tubes etc that I was desperate to get the cannula removed, so at that point I wished I hadn't participated. However, I do feel that contributing to the research has been worthwhile"*
Side effects	17	*"The feeling when the drug was initially administered was very frightening, felt like my whole body was bursting into flames"* *"I knew I was given the drug as I got so hot and it felt terrible"* *"During the caesarean my blood pressure dropped and I felt faint so the infusion was stopped"* *"I felt really awful after having the magnesium sulphate, cause my blood pressure went really low"*
Birthing experience	10	*"Because the child's birth was hard and the trial seemed like it was dragging it out"* *"I didn't enjoy the trial but I think it is important to try and find any remedy that would help ease / stop pre-eclampsia"* *"As far as I remember taking part slightly delayed the induction/caesarean/recovery process"* *"As the birth of my daughter was early and unexpected a lot seemed to happen very quickly at the hospital, being hooked up to all the monitors and drips wasn't my idea of a perfect birthing situation, also after the birth it was a long time before I could be taken off all the drips etc"*
Other themes	4	*"I didn't say definitely because I was scared It might harm the baby"* *"I probably would but I might not have had this much pain now if I didn't go through it. I don't know if that is why but it's a chance you take"* *"I am not definite as the reaction I had when received drug has put me off, although I am not sure whether it may have been nerves etc to giving birth as opposed to the trial"*

Table 4.5 Explanation of women answering 'probably yes'

Not sure:

Of the 34 (5%) women that chose this option 21 (62%) gave an explanation in the free text section as to why. The most overwhelming reason was related to the difficulty of their situation. As pre-eclampsia is often asymptomatic, many women had no prior indication of their illness, and knew little about it. Some women were therefore asked to join with little prior warning and as a consequence were feeling particularly frightened and distressed, and this was, essentially, in relation to having severe pre-eclampsia and needing

emergency care. A few women appeared to choose this response option because they had little understanding or recall of the Magpie Trial:

Theme	Comments (n)	Sample of women's comments
Circumstances at time of recruitment	9	*"I was approached in hospital at a very traumatic time on the day I was admitted urgently. I didn't feel in a position to make an informed choice and to ask many questions as I was overwhelmed at the time"* *"It was difficult to make an informed decision when exhausted and having severe labour pains coupled with high blood pressure. I therefore felt bullied into it"* *"I can't remember much about it when I had her. I remember being explained to but I was upset at the time about pre-eclampsia and felt very upset and worried"* *"At the time I did it because I was in danger. I did not have enough time to think about it to be honest. If you ask me what it is I do not have a clue because I did not understand what they explained to me at the time"*
Limited understanding of trial	6	*"I would like to know in exact detail what was being offered to me and what it actually does to relieve pre-eclampsia i.e. how it works on the body"* *"I don't know anything about the Magpie Trial. I don't know what it is, what it's for except pre-eclampsia and I don't know whether it has any side-effects"* *"I still don't understand"*
Long-term effects	2	*"I still have high blood pressure"* *At the time it was something I didn't have much time to think about, and up until recently haven't thought much about, but since trying to conceive again, without any luck so far, I am now a little concerned that perhaps agreeing to take part may have had some effect on my being able to conceive"*

Table 4.6 Explanation of women answering 'not sure'

Probably no:

Of the 23 (4%) women that chose this option, 21 (96%) gave an explanation in the free text section as to why. Occurrences of unpleasant side effects caused by the trial were the most prominent reason given. The remaining explanations given by the women identified their misunderstandings regarding the nursing care they received. It was apparent they, incorrectly, perceived that many of the unpleasant procedures (clinical monitoring, oral fluid restriction) they experienced were attributable to the trial:

Theme	Comments (n)	Sample of women's comments
Side effects	14	*"At the time I was so willing to try anything, I was so poorly. But as soon as the trial was injected into me my whole body burned. I remember crying in pain, then it was tried again to make sure of the same result. So I wouldn't do it again"* *"I suffered from migraines and nausea while I was on the trial. I felt this had something to do with it"* *"Because it didn't agree with me, I felt like it was burning my chest and I was having difficulty breathing"* *"Whilst I was on the trial I experienced severe burning all over my body. I was delusional; I didn't know what was happening to me. My midwife insisted it was to be stopped immediately because of the state I was in"*
Mixing clinical care with trial	6	*"When asked if I would like to take part in this trial I asked 'Would it interfere with my labour?' and I was told 'no'. This was not the case – it did! For three days I was catheterised and had drips, could not even have drinks, never mind food. Very tiring and unpleasant"* *"The checking of blood pressure etc in the 24 hours after child was born prevented me from being with her and feeding her"* *"I had to remain in hospital for 24 hours when I wanted an early discharge and this had not been explained to me properly"* *"I already had a lot of things going on e.g. B/P monitor, morphine etc I seemed to have a lot more tests and more needles in me after agreeing to do the trial"*

Table 4.7 Explanation of women answering 'probably no'

Definitely no:

Of the 33 (5%) women that chose this option, 30 (91%) gave an explanation in the free text section; their explanations were largely similar to those of women who responded 'probably no'; the experience of unpleasant side effects (n=9) and confusion relating to care received as part of the trial (n=15) being most frequently reported. The additional themes that emerged related to difficult and unpleasant incidences relating to clinical staff and the care they received:

Theme	Comments (n)	Sample of women's comments
Negative experiences	11	*"I did not like how the consultant treated me, he didn't explain things fully and I felt pressurised and like I was just part of an experiment, not a person just a guinea pig!"* *"Too much time was spent by the midwife completing forms that I felt I was neglected"* *I felt I was pressurised by the midwife to join the trial. After the birth I suffered other 'life threatening' problems and the midwife did not even call to see me on the ward"* *"Staff did not know what to do to administer the trial, and due to pre-eclampsia and other complications, they had too many recordings of information to do. The trial was discontinued due to a mistake with the vials and overall the staff were relieved and withdrew. This added to the stress of an already stressful situation. If I was sure it would not add to the stress of the situation I would happily take part in further / other trials"*

Table 4.8 Explanation of women answering 'definitely no'

The second and third questions in the postal questionnaire asked the women to record in their own words anything that could have been done to improve their experience of joining (Question 2) and anything that was particularly good about joining the trial (Question 3). The next section presents the findings from these questions.

4.3 Responses to question 2

4.3.1 Q2 – 'Please tell us if there was anything about the Magpie Trial you think we could have done better'

Based on their responses to this question, most women joining the Magpie Trial appeared to be generally satisfied with their experience of joining. A large proportion (n=144; 44%) of women stated that nothing could have been done better: *"No, everything was done really well" "Nothing, it was excellent!" "I think it was all handled very well, including the follow up"*

Nevertheless even women who were generally satisfied with their experience, in that they responded 'definitely yes' or 'probably yes' to the first question, gave suggestions about how the trial could have been done better. Similar suggestions were made by women who responded 'not sure', 'probably no' or 'definitely no'. The women's suggestions were divided into four themes (see Table 4.9):

(i) content of the information at recruitment:

It appeared some of the women were dissatisfied with some aspect of the explanation they received about the Magpie Trial. The main difficulties expressed by the women included lack of detailed information provided about the trial by clinicians, the timing of when the explanation was given, and some women preferring the trial information in a more detailed format.

(ii) timing of the approach to join the trial:

Women eligible to join the Magpie Trial had a severe form of pre-eclampsia, which is extremely dangerous and can be life threatening. The majority (78%) were recruited whilst pregnant and a third were less than 34 weeks gestation. Women could be, and were, recruited up to 24 hours after delivery. Women

were therefore extremely ill, most receiving high dependency intensive care. Informed consent to participate in the Magpie Trial was sought then at a time of great anxiety for the woman. Women were vulnerable, and for most they had the extra responsibility of being pregnant.

(iii) wanting to know treatment allocation:

Wanting to know the allocated trial treatment was important for some of the women. It was apparent from their responses they thought that this should be provided routinely by trialists. Requests to have this information were made in some of the questionnaires, and the unblinded information was then sent to the women by post.

(iv) wanting to know the trial results:

Members of the Magpie Trial management group felt it vital to provide the results directly to the women involved on completion of the trial. The ethos of the trial was to acknowledge the central role the women had in the trial, to promote their involvement and encourage partnership and collaboration between the women, the clinicians and the trialists. Requests to know the Magpie Trial results were made in the questionnaire. A summary of the results was sent by post to all women included in the follow up; for some; however, this was after their questionnaire had been sent. The following responses illustrate these themes:

Theme	Comments (n)	Sample of women's comments
Content of information provision	61	*"I could have been given more information by hospital staff when told I had pre-eclampsia"* *"Maybe more information, because when I was asked I was unaware of my condition, so maybe if they had come back and talked more about it when I was well. To be honest I was a first time mum and it was all a bit new to me and it was a bit of a shock"* *"I think it could have been explained a lot better. I was just given some leaflets to read and then asked to make my decision"* *"I could have done with some more literature. Not enough information – all a bit of a rush"*
Timing of approach	46	*"I cannot remember exactly when I was asked to join the trial, but think it was immediately before or after an emergency section. As I had already been diagnosed with pre-eclampsia some days before, I would prefer to have been approached earlier at a less stressful time"* *"It should have been explained earlier at admission, before I became very unwell"* *"Explanation could have been better i.e. more information and timing, would have preferred to know about the trial earlier on in pregnancy, rather than just before the caesarean section"* *"If possible ask mothers earlier on in pregnancy that if they were to develop pre-eclampsia or signs would they take part in a trial. Earlier rather than during labour when they've been told that have signs of pre-eclampsia"* *"I would have been preferred to have been asked earlier (not when in labour) so I had a little more time to ask questions and make a more informed choice"*
Requesting unblinding	9	*"I feel that it is better to inform the patient after the trial what they had, whether they were given either placebo or magnesium sulphate"* *"Can we know what drug we had for the trial? i.e. control or magnesium sulphate"* *"It would be nice to know if I was given magnesium sulphate or the placebo"* *"I think telling the patient whether or not they were taking the magnesium sulphate would help to stop people wondering or worrying"*
Wanting to know results	7	*"I would have liked to have received more information about the trial and maybe some pre results if possible"* *"I don't think anything could have been better but it will be really interesting to know the findings "* *"I would like to know the results"*

Table 4.9 Women's suggestions for how the Magpie Trial could have been done better

4.4 Responses to question 3

4.4.1 Q 3 – 'Please tell us if there was anything about the Magpie Trial, or your experience of joining the trial, that you think was particularly good'

Responses women gave to this question were categorised into six broad themes:

(i) The Follow up Study:

Irrespective of the women's response to question 1, they were extremely positive about being followed up after the trial and receiving trial results. Long-term follow up of research participants does have the potential to cause anxiety and distress. Overwhelmingly, however, the women responding to this question confirmed how much they welcomed this.

(ii) Feeling altruistic:

Some women considered joining the trial had the potential to benefit others, and this was perceived as something they valued.

(iii) Good nursing care:

Women were grateful for the nursing care and kindness they received whilst in hospital. Many confirming this helped with what was a difficult and stressful experience.

(iv) Explanation about the trial and pre-eclampsia given by the staff:

Women appreciated the detailed information provided about the trial and about having pre-eclampsia. In discussing the trial with clinical staff women said they learned more about pre-eclampsia than they would have otherwise.

(v) Benefit to self:

It was evident from the women's responses that many considered there were benefits to be gained from joining. These were mostly related to the trial helping to minimise the associated risks of pre-eclampsia.

(vi) Receiving trial results:

Appreciation of receiving the Magpie Trial results was noted by the women as being particularly good.

Theme	Comments (n)	Sample of women's comments
Being followed up	105	*"I think keeping in touch after the birth is a good idea to see how people are"* *"The follow up contact and interest was and is both unexpected and most welcome"* *"I have appreciated this follow up and knowing that I have contributed and wasn't forgotten"* *"I am particularly impressed with the follow-up information and surveys I've received"*
Benefit to others	52	*"It's just a nice feeling knowing that you could be helping out other pregnant women with the same condition as myself in the future"* *"Mainly that I'm helping others"* *"If the research is to help expectant mothers with toxaemia in the future then it has got to be a good thing"* *"Just being part of something that has helped others"*
Positive experiences with care received	46	*"Whether it was because of pre-eclampsia or 'normal' care at the hospital I will not know, but I felt safe in the fact that I was closely monitored and not left alone in labour and after the birth checked every 20 minutes or so"* *"Care throughout trial whilst in hospital"* *"I thought the care of the nurses was very good"* *"Supervision, there was always somebody closely monitoring me"*
Explanation given about the Magpie Trial	40	*"The care from the midwife involved, I was told exactly why it was being done and how it would help"* *"I was really scared at first, but the hospital was good and explained everything, and I didn't hesitate to help out"* *"I was well informed and the doctors talked about it for a while answering loads of questions we had"* *"The explanation and information given and the approach to the trial, staff knew what was involved and gave explanations and answered questions fully"*
Benefit to self	20	*"Only that it may have prevented eclampsia"* *"Possibility of reducing fitting"* *"I felt that it maybe stopped me from having a fit, so the recovery from the section could have been a lot longer"* *"It may have saved my life and my son's life"*
Receiving trial results	12	*"The fact that you will let us know the results in the future"* *"Finding out the results afterward; knowing that the trial may prevent some tragic incidents in the future has to be a good thing"* *"Being kept informed of results"* *"Results made widely publicly available"*

Table 4.10 Women comments on what was good about the Magpie Trial

4.5 Conclusion

The main objective of the follow up study questionnaire was to find out whether magnesium sulphate affects the woman's longer-term risk of death or serious morbidity. All those who remained part of the follow up study (761) were sent the questionnaire; a response was received from 81% (619). The postal questionnaire gave women the opportunity to express their views regarding participation in the Magpie Trial. The use of fixed response options, together with space for additional free text, where women were invited to

explain their choice of response, provided a unique insight into their experiences around the time of recruitment to the Magpie Trial.

Overall the findings from the trial experience questions confirm that the majority (85%) of the women were happy with their participation in the trial. The women were recruited at a time when they were likely to be having intensive monitoring, and there was often a concern about the health of the baby as well as themselves. Although care attributed to Magpie was small, many of the women appeared to have difficulty in separating out what was their experience as a direct consequence of joining the Magpie Trial and what was linked to the facts of their pregnancy and to having pre-eclampsia. This was most evident for those women who were dissatisfied with some aspect of their trial experience. These women often interpreted aspects of the nursing procedures and monitoring of their pre-eclampsia as being connected to the Magpie Trial itself. This resulted in them often interpreting the trial in a negative way.

Some women described negative experiences of taking part relating to experiencing unpleasant side effects. For others it appeared they were generally less satisfied by their overall birthing experience, which was probably not attributable to the trial itself.

The findings from the postal questionnaire enabled a large number (n=619) of women throughout the UK to express their views regarding participation in the Magpie Trial. Furthermore the high response rate to the questionnaire demonstrated that the use of this method and the format of the questions were acceptable to the women. Following completion of this questionnaire, a sub-set of the women were then offered the opportunity to take part in a semi-structured interview to find out, in more detail, about their experiences of joining the trial. Data from these interviews are presented in the following four chapters.

Chapter 5

Introduction to the findings from the QUOTE Study interviews

5.1 Introduction

This chapter is the first of four providing a detailed presentation of the findings from the semi-structured interviews. The purpose of the chapter is to act as a precursor to the following three results chapters, which present the thematic analysis of the in-depth qualitative interviews. The chapter provides summary background information regarding the interviews performed. It begins with presenting an overview of the provision of trial information the women received, including the timing of this provision. A brief description is then presented regarding the conduct of the interviews. Profiles of the forty women interviewed are then provided. All transcripts were subjected to thematic analysis; the chapter concludes with presenting the identified themes, which are discussed in detail in subsequent chapters (6 – 8).

5.2 Interviews conducted

Fifty women were offered an interview and ten declined: six having had a home visit and four having not. All those who declined were recruited while still pregnant; three of their infants were admitted to the neonatal intensive care unit after birth. For those refusers who had a home visit all were healthy, four of the children had screened positive on the ASQ, but were later found to be developmentally normal.

The interviews were carried out at different time points after recruitment to the trial. Although the follow up study aimed at assessing children at two years of age, this was not always the case, as follow up did not start until after the main Magpie Trial was complete. Hence the interval between randomisation and interview was greater for those women who were recruited early in the trial. Timing of the interviews also depended on completion of the follow up study postal questionnaire, as women could only be contacted and offered an interview once they had completed their questionnaire and for the majority this was also after their follow up study

home visit (n=30). Time points therefore ranged from two years to four years and seven months (mean time three years and one month, SD±9.57 months). For those women who had a home visit performed (n=30) the interview took place on average eight weeks later. The interviews took place from September 2002 to May 2004. In all but one, women were interviewed alone, for one woman (aged 16 at the time of recruitment) her mother was also present at the interview at her request and participated throughout. All interviews were performed in the women's homes. They lasted between 30 and 120 minutes (mean time 50 minutes, SD±20.91 minutes), and all were tape-recorded with the permission of the women.

A concern for this study, as previously discussed, was having all the interviews performed by myself (research midwife for Magpie Trial). It was recognised that this might make it difficult for some women to talk honestly about their experiences of joining the trial, especially if they had a negative experience. In order to lessen this effect, another interviewer (LW), who had no involvement with the Magpie Trial or the QUOTE Study carried out some (n=10) of the interviews. At intervals we both met to read over each other's interview transcripts and discuss similarities and differences. Interviews were also compared in relation to any negative aspects expressed by the women about their experience. I found no variations in the answers given by the women that could be attributed to giving more desirable responses to me than to any non-involved colleague.

Prior to the interviews being performed the main Magpie Trial results had been published (Magpie Trial Collaborative Group 2002), to considerable media coverage. At the time of the interviews a lay summary of findings were posted to all women (Appendix 6). As a consequence all women interviewed were, in principle, aware of the trial results. However, in practice, it was evident some women had either not received the trial results (n=3) or could not recall receiving them (n=3). At the point of interview both interviewers were blind to treatment allocation. The women, however, had been previously informed they could request information regarding their treatment allocation by writing to the trial co-ordinating centre. Three women had done

so and therefore were aware of their trial treatment at the time of the interview.

For most women the interview was the first time they had been asked to recall in depth their experience of participating in the Magpie Trial, although all women had received reminders of the Magpie Trial through the follow up study prior to the interview. Receiving the postal questionnaire and a home visit had triggered many to talk to family members about the trial again. However, they had not been asked to re-consider their understanding or reasons for joining. It was evident from the interviews that although the trial was important at the time of joining, many had given it little thought since. Asking the women to recall this event in some detail made it necessary to clarify with the women what they understood at the time, what they had learnt since and explore what they might have forgotten. It was apparent from conducting the interviews and listening to the transcripts that women would sometimes contradict themselves, for example describing the decision to join the trial as 'difficult', yet at another point in the interview stating the relative 'ease' of joining. These contradictions highlighted the complexity of the situation experienced by the women, both at the time of joining and also at the time of the interview.

The interview schedule (Appendix 9) asked the women to recall the events surrounding the Magpie Trial in a chronological order. The interview began with asking the women to describe their circumstances and their reactions to being diagnosed with pre-eclampsia, through to being involved in the follow up study some years later. However, as with any conversation there were diversions throughout. It was evident in the interviews that one issue would prompt another, which was unrelated in the interview schedule, but not for the women themselves. This made thematic analysis and presentation of the results sometimes challenging; and some quotes have been presented twice in separate sections of the results because they were judged to illustrate more than one identified theme. The discussions between the clinicians and the women at the time of consent were not observed or tape-recorded, nor

were the clinicians asked for their accounts. Therefore, the description of what took place is based solely on the transcripts from the interviews with the women.

There was a time gap of about three years between recruitment in Magpie and the QUOTE Study interview and this might have affected the women's recall. Studies of women's memory of labour and birth have generally concluded that recall is fairly accurate (Olson et al 1997, Niven and Murphy-Black 2000, Waldenström 2003). In one of the few studies of women's long-term memories of childbirth as a comprehensive experience, Simkin asked 20 first time mothers to complete a questionnaire, including an open-ended account of labour, shortly after birth and 14 to 20 years later, and the women were also interviewed after the second questionnaire (Simkin 1992). The researcher concluded that, years after the birth, women's memories were generally accurate, despite a decrease of material recalled from the first to the second questionnaire and some lapses or errors in memory of specific details. She also found that the significance women attached to negative events seemed to intensify and increase over time, whereas the positive aspects remained consistently positive in most women.

5.3 Characteristics of women interviewed

Sampling for the interviews was not aimed at trying to produce a statistically representative sample of the overall UK trial population. Instead, a purposive sampling matrix incorporating key characteristics (described in Chapter 3) was used. Data were collected on characteristics at trial entry and outcome after randomisation for all the women interviewed; and compared with UK women overall (Table 5.1). The women interviewed were recruited from six selected maternity units in England (three in the north west, two in Yorkshire and one in the Midlands) as well as different treatment arms of the trial (22 magnesium sulphate; 18 placebo). They were aged from 16 to 39 years (mean years 29). Detailed individual characteristics of those interviewed are presented in Appendix 10.

When comparing characteristics at trial entry and outcome after randomisation there were some differences for the women interviewed and those not. Although differences were not statistically significant, a higher proportion of women interviewed were randomised to the trial postnatally than those not interviewed 27% versus 22% (Relative Risk (RR), 1.31 Confidence Interval (CI) 0.64 to 2.69); had had a caesarean section 76% versus 60% (RR; 2.08; CI 0.87 to 4.97); had their labours induced 72% versus 56% (RR; 1.45; CI 0.77 to 2.76); and were recruited before 34 weeks gestation 38% versus 34% (RR; 1.07; CI 0.52 to 2.19). Mainly due to purposive sampling, a higher proportion of women whose children screened positive on the ASQ were interviewed compared with women not interviewed 60% versus 29% (RR; 5.18; CI 2.67 to 10.04).

	Interviewed		Not interviewed	
	n =40	(%)	n=579	(%)
Characteristics of women				
Primiparous	30	(75)	423	(73)
Multiple pregnancy	4	(10)	25	(4)
Age (less than 20 years)	2	(5)	46	(8)
Severe pre-eclampsia	23	(57)	261	(45)
Imminent eclampsia	9	(22)	157	(27)
Delivered before trial entry	10	(27)	127	(22)
Randomised magnesium sulphate	22	(55)	281	(49)
Outcome after randomisation – maternal				
Eclampsia	0	(0)	4	(<1)
Other severe morbidity				
Admission to high dependency care	36	(90)	485	(84)
On trial treatment more than 12 hours	31	(78)	486	(84)
Side effects	10	(25)	102	(18)
Randomised before delivery	29		448	
Caesarean section	22	(76)	269	(60)
Induction of labour	21	(72)	250	(56)
Outcome – Infant				
≤34 weeks at trial recruitment	11	(38)	152	(34)
Admitted to neonatal unit	17	(43)	308	(68)
ASQ Screen positive*	24	(60)	130	(29)
Response to postal questionnaire				
Would you join the trial again: Definitely yes	21	(52)	335	(58)
Probably yes	10	(25)	156	(27)
Not sure	3	(7)	31	(5)
Probably no*	4	(10)	19	(3)
Definitely no	0	(0)	32	(5)
Not answered*	2	(5)	2	(<1)

* Statistically significant when comparing those interviewed with those not

Table 5.1 Characteristics of women interviewed and not interviewed

5.4 Provision of trial information

Of women recruited to the Magpie Trial in the UK (n=804), most (78%) were pregnant at the time, just over half (57%) had their labours induced, and two thirds (61%) were delivered by caesarean section. The decision to deliver women within 24 hours of recruitment to Magpie was often made by the recruiting clinician. As a consequence over a quarter (32%) of women delivered their babies preterm (less than 34 weeks gestation), often resulting in increased levels of mortality and morbidity.

Most women interviewed had been recruited to Magpie whilst they were on the delivery suite or high dependency unit. Although the decision to offer trial participation was made by the obstetrician, either an obstetrician or a midwife could recruit women. Recruiting clinicians were supplied with trial information leaflets (Appendix 16) to distribute to eligible women as part of the informed consent process. An additional leaflet, 'Do you know about pre-eclampsia? (Appendix 17), was also provided. This supplementary leaflet included information about pre-eclampsia developed by a user group, Action on Pre-eclampsia (APEC), and provided the APEC telephone helpline number. The final paragraph introduced the Magpie Trial. The distribution of both leaflets was at the discretion of the individual recruiting clinician, in the UK centres were encouraged to provide information about the trial at booking. The Magpie Trial team also provided posters to be displayed throughout the recruiting hospitals. Some were prepared for the women and so put on view in clinic waiting rooms and on the antenatal wards. All were displayed at the discretion of the individual hospital.

Before exploring the women's perceptions and understandings of the trial it was necessary to establish where and when they recalled receiving trial information.

5.4.1 Written information:

Of the 40 women interviewed; 28 recalled being given the Magpie Trial information leaflet at the time of recruitment; eight reported they did not recall seeing the leaflet at any time; and four women were unsure. Nineteen

women stated that they had read the information leaflet at the time of recruitment, although of those three felt that due to the difficult circumstances at the time they could not comprehend the information. Eight women reported they did not read the leaflet at the time of recruitment, though, for two of these women their partners did. One woman did read the leaflet but only after agreeing to join the trial. None of the remaining women recalled seeing the leaflet. When shown the additional leaflet 'Do you know about pre-eclampsia?' none of the women recalled seeing it. One woman recalled seeing a poster about the trial in the waiting area of the delivery suite prior to being admitted.

5.4.2 Oral information

At the time of recruitment the majority of the women (n=30) were spoken to by a midwife about the trial; for six this was in conjunction with the obstetrician. The obstetrician discussed the trial with ten women. Most women (n=38) recalled hearing about the trial for the first time while they were being cared for in a high dependency unit (situated on the delivery suite), either while in labour, or having their labours induced or moments before having a caesarean section. The remaining two women were on an antenatal ward.

5.5 Themes identified from the interviews

Data from the interviews were subjected to thematic content analysis. From the analysis a number of major but related themes emerged. These themes were combined into five broad categories.

Categories	Themes
1. Circumstances around time of recruitment (presented in Chapter 6)	i) Speed of clinical situation ii) Unpredictability of pre-eclampsia iii) Difficult time to be approached
2. Women's understanding of the Magpie Trial (presented in Chapter 6)	i) Purpose of the Magpie Trial ii) Implications of joining the Magpie Trial iii) Appreciation of possible risks from joining iv) Mixing clinical care with the trial care
3. Methodological principles of randomised trials (presented in Chapter 6)	i) Random allocation ii) Equipoise iii) Use of placebo iv) Treatment blinding v) Thoughts on treatment allocation
4. Women's views regarding the decision-making process (presented in Chapter 7)	i) Making the decision ii) Difficulty with asking questions iii) Voluntariness of joining iv) Influences on decision-making v) Quality of information received vi) Involvement of others in decision-making
5. Women's reflections of joining the Magpie Trial (presented in Chapter 8)	i) Receiving the Magpie Trial results ii) Experiences of the follow up study

Table 5.2 Themes from interviews

5.6 Coding of quotations

To ensure anonymity and confidentiality each woman interviewed was assigned an individual number and all quotes were anonymised. To provide the reader with additional data regarding individual women's profiles, a coding system was devised demonstrating key characteristics of the women concerned. Initially codes were linked to the pre-specified characteristics that had been thought likely to influence the women's perceptions of their experiences and recall of the Magpie Trial (as discussed in the previous

chapter). However, there was no apparent effect of two of the characteristics - the child screened (by the ASQ) as having some degree of development delay, and the woman herself having persistent hypertension since joining the Magpie Trial. Both appeared unlikely to influence the women's perception of trial experience, the infrequency of both events being the main reason. However, being recruited to the Magpie Trial while still pregnant *did* influence women's experiences. Unsurprisingly, in the qualitative analysis it became apparent that there was a link between women's responses to Question 1 in the postal question, which asked the women whether they would agree to participate in the Magpie Trial again, and their perceptions of the trial. Therefore, the women's responses to this question were incorporated into the codes.

Thus, individual codes used denote three factors:

- Interviewee number (01-40)
- Whether the woman was antenatal or postnally recruited (AN or PN)
- The woman's response to postal question 1 (definitely yes, probably yes, not sure, probably no, definitely no)

An example of an individual woman's code would be: 07, AN, probably yes. This denotes interviewee number '07', who was recruited 'antenatally' into the trial, and stated 'probably yes' she would join the Magpie Trial again to question 1.

5.7 Conclusion

The chapter has set the scene for the qualitative interviews by providing background information regarding the forty interviews performed. Profiles of the forty women have been presented together with a description of the conduct of the interviews and an overview of the trial information the women received prior to joining, including the timing of this provision. The chapter concluded with presenting the identified themes. The next three chapters (6 – 8) present detailed interpretation of the qualitative data in relationship to the identified themes that were generated from the interviews.

Chapter 6

Women's interpretation of the Magpie Trial

6.1 Introduction

This chapter deals with three of the categories detailed in Chapter 5 (Table 5.2): the circumstances around the time of recruitment; women's understanding of the purpose of Magpie Trial; and their understanding of the methodological principles of randomised trials. Verbatim text from the interviews is given throughout (in order to allow the reader to scrutinise my interpretation of the data) The chapter also includes discussion and consideration of how the women's experiences compare with those reported in previously published literature. Each quotation provided is selected for its ability to represent and support the identified themes. The number of quotes displayed reflects the huge amount of data the interviews produced. Because of this and in order to aid reading of these sections, not all quotes that relate to a particular theme have been presented. However, additional supporting quotes are reproduced in Appendix 18 (this applies to chapters 7 and 8 also).

6.2 Circumstances around time of recruitment

As previously noted, informed consent to participate in the Magpie Trial was sought at a time of great anxiety for the women. Women were often extremely ill and receiving high dependency care. The majority of women interviewed were recruited while pregnant (n=29) and still a number of months before their expected delivery date, although women could be, and were, recruited up to 24 hours after delivery. Fifteen of the women were in established labour when recruited to the trial, and therefore likely to be experiencing some degree of pain. Most women giving birth use some form of pain relief during labour, and four of these women confirmed they received narcotics. Two women had their labours induced: seven were recruited shortly before having a caesarean section, three whilst having their condition stabilised on high dependency unit and two had been admitted for observation on the antenatal ward. Three women were approached just after

delivering their baby. Just under half (n=16) of the women who were interviewed were recruited to the Magpie Trial in the evening or at night time.

As previously discussed, due to the difficulty in detecting pre-eclampsia, and the fact that most women experience no symptoms until they have severe disease, there is often no advance warning of the condition. The interviews confirmed that most (n=25) women had become acutely ill unexpectedly and in a very short period of time, and so were required to make their decision to join the trial relatively quickly. Most (n=33) reported consent to participate in the Magpie Trial was at a time of immense worry and distress for them.

6.2.1 Speed of clinical situation

It became apparent in the interviews that the clinical circumstances around recruitment had had a considerable effect and were an integral part of the women's trial experience. Although there were some differences in the views and experiences of the women, there was much common ground. Many identified difficulties they faced being approached by the clinicians to discuss the trial, which they stated were exacerbated by the fast moving and frightening circumstances they found themselves in. There was evidence of helplessness in their responses, the women feeling scared for themselves and their unborn baby, as well as feeling powerless and vulnerable. The clinical situation undoubtedly contributed to what was already a complex decision-making process. The women also expressed problems associated with being unprepared due to the unpredictability of pre-eclampsia:

> "They were running around like headless chickens at times, and there were so many people." [15 A/N prob no]

> "I had so many people around my bed, I don't really remember. I had all sorts of people doing all sorts of things. I cannot really remember. I know there were midwives there. It's not like being asked to join a trial when you are well is it? You are being asked to join a trial when you could die, basically. Quite a hard thing, I don't know how you can make it better, but it is a hard thing to do when you are ill." [09 A/N prob yes]

"I was just taken into a room with my husband and they just said 'we need to get your blood pressure down'. They didn't have time to explain what was going to happen, they just put in the catheter and all the needles and I have never had a baby so you don't know, I thought I had food poisoning at first. The next minute they did the scan for the baby while I was all wired up and then they said that 'we should ask your mum and dad to come up' and I said 'no, no, I'll be fine' and then what scared me more was one of the nurses said 'I think we should telephone her parents' that frightened me a bit. It was very frightening, in a matter of seconds there were doctors and nurses around me that was very frightening and while they were doing, you know, putting needles in me, and so on, no-one was really talking it was very silent and I was frightened to ask because you don't want hear the word because my husband was there and he was upset and you're frightened to say what's wrong just in case they say the baby hasn't survived that's what is going through your head, everyone was very silent." [25 A/N def yes]

"As it was someone was attaching you to a monitor, someone was asking you to do the trial and someone was attaching you to a drip. I think it should definitely be explained a bit more and I do feel that you don't ask questions because you have got high blood pressure and everyone is rushing round you just leave people to get on with the job and I know that I felt, not intimidated, but you don't want people to get fed up with you if you ask too many questions, you just want everyone to stay on good terms, you don't want everyone to think 'oh god here she goes again!' So you keep quiet. If it had been my second or third I wouldn't have felt like that, I would have just asked the question." [29 A/N not answered]

"I wasn't in a position to read anything. It was very quick and my main concern and the nurse's were to get my blood pressure down so I signed for it." [30 A/N prob yes]

"Yes I signed a consent form. I recall him telling me what it was about but at the same time I had a paediatrician telling me what the odds of the baby surviving were, so that took priority." [28 P/N prob yes]

One woman describes the moment she gave consent:

> "It [*Magpie Trial*] was first mentioned when we were actually down in the delivery suite. The blood pressure had gone really, really high they rushed me down. You appreciate it's serious but I think you sort of gather that the way all the clinical staff are running around like headless chickens. When it happens, something serious happens, the alarms go off, you know so many people die, you think crikey! It's like when you are signing a form for a section *[caesarean]*, you would sign anything at that point. The thing is you are in a room there are machines all over the place, and you're wired up, we knew things were not right. So it was a case of just get on with it." [01 A/N Def yes]

6.2.2 Unpredictability of pre-eclampsia

The unexpectedness of pre-eclampsia, and having little prior understanding of the condition appeared to exacerbate this difficult and often frightening situation for the women. Most women implied their understanding of pre-eclampsia was poor, a better understanding would have helped, and this in turn made the decision to join the Magpie Trial even more difficult:

> "I do not think you could have made it easier at that time because I was ill. I only had a few weeks to go. I do not think there is enough about pre-eclampsia. I mean I had an idea, but pre-eclampsia was not mentioned. If you give more information on pre-eclampsia that would be useful. Even in the antenatal classes there were no posters on it." [34 P/N prob no]

> "I had regular once a week check-up but my blood pressure was fine, but then it just went suddenly. It was not a gradual thing it just went. At 32 weeks it just started to go really quick. I had not a clue what it was about. Just your blood pressure went high and you got protein in your urine. I had not got a clue that it was potentially fatal. I did not know any of that. It would have been nice for someone just to sit down and give me some figures and explain women die of it. I did not have enough information in that way." [19 P/N def yes]

The doctor said we will monitor you for a few days and see how it goes, then about five minutes later she said we need to get the baby out now! We are going to induce you." [30 A/N prob yes]

6.2.3 Difficult time to be approached:

When asked about their experiences of considering joining the Magpie Trial, the most frequently raised issue was the timing of information provision. For most women (n=38), the first time they had heard about the trial was when they were seriously ill and were being asked to consider joining. Many women felt they were unable to think clearly and process the trial information; having to make a decision at a time when they had a life threatening illness, sometimes exacerbated by labour (n=15), compromised their capacity to appreciate what they were being told.

Most women would have preferred to know about the trial prior to the point at which they had to make a decision to join; and felt that had they been asked earlier they would have had a better appreciation of the purpose of the trial. Women suggested they would have had better understanding and been more satisfied with the information if this had been provided antenatally. By having it in advance they felt they would have more time to consider the implications and the opportunity to ask questions:

"I remember being asked about it, but I was so much out of it at the time. The way the midwives and doctors ask women to take part in research. I really don't think they should ask you when you are in the late stages of labour and about to give birth. I think you should be asked in the early stages of pregnancy and given information in case you are asked to do it. So that you are fully aware of what you are getting into at the time." [30 A/N prob yes]

"Maybe when you are not so poorly mentioning it. At the initial stage when you go and see the midwife at first, then it would probably stick in your head a bit more. Like when they do the test for Down's Syndrome maybe that could be part of when they go through all that with you as well. It may be good to be told about it at the beginning of the pregnancy rather than you

giving birth and you are really poorly or you are on drugs so your head is not quite there. Maybe if they told you early on in the pregnancy 'if this does happen then we can give you this'." [23 P/N prob yes]

"Possibly in the antenatal clinics it might have been an idea to bring it up. I don't know whether they do that and I had just missed it and was not aware of it, but it might have been good to have it in the notes *[handheld maternity case records]*." [27 A/N prob yes]

"I think put the leaflets in packages earlier. Maybe at antenatal clinic, if the leaflets are in the antenatal brochures earlier and you get a chance to read about it then you can ask the midwife when you go. If you are interested you could sign up there and then." [34 P/N prob no]

These suggestions are supported by the study of East and Colditz (1996) who developed a questionnaire to evaluate women's perceptions of their participation in a research project of fetal oxygen saturation monitoring during labour. Women stated being told about the trial while in labour was difficult and they would have preferred to be told about it during their pregnancy. Smedstrad and Beilby (2000) advise that written information regarding intrapartum interventions such as epidural anaesthesia should be distributed in antenatal clinics, so women can read them at leisure. They propose they should not, however, replace the informed consent discussion, but be an adjunct to this process.

Observational studies of communication between midwives and women antenatally (Levy 1999) and during labour (Kirkham 1989:117) have highlighted both the importance of giving adequate information and the misunderstandings that can occur when communication is poor. More recently there have been steps in some maternity hospitals to provide, as the above women suggest, all pregnant women with information in the antenatal period about ongoing in-house research. The Magpie Trial did make available antenatal information for women, but it appears from what the

women said that the leaflets may not have been made available to them at all the participating hospitals, or that the women had forgotten seeing them.

Some women, however, did appreciate the justifiable limitations of the clinicians in being able to predict which women would become ill with pre-eclampsia and therefore be eligible for the Magpie Trial. A substantial number of women interviewed acknowledged the difficulties associated with the provision of trial information in their particular circumstances and appreciated that giving information prior to the event was not necessarily a viable solution. There was an awareness by some women that there can be no 'best' time to give this information, since earlier provision could have caused unnecessary worry:

> "I don't think there is really, because it can't be like the midwife that you see for your antenatal things because they are not based in the hospital. It has to be a midwife based on the delivery suite and you don't really know because you only go in there when it's actually happening." [01 A/N def yes]

> "I don't know what is the way round it. They couldn't approach me when I was at home and nobody knew I had pre-eclampsia so it is a difficult time to ask someone if they want to be part of a trial, any sort of a trial." [04 A/N prob no]

> "There is no perfect time to ask someone to take part in this research. No one knew I was going to get sick, so I could not have been asked earlier. Maybe I could have been aware that there were certain trials going on when I was pregnant. Maybe I was, maybe they did give me a list. Maybe there could have been more information, but then maybe I would not read it anyway." [31 A/N def yes]

Women also appreciated their own fears of being faced with knowing in advance what could happen to them in their pregnancy:

"I don't think there was any alternative for me. I do not think you could have asked me any earlier. If someone had suggested six or eight weeks earlier that this was going to happen to me, then somebody could have come, I suppose that would have been lovely, but there was no suggestion that I had anything wrong. The local midwife I think should have given me a bit of information about the trial. Yet, I think if someone would have said when I was two months pregnant this trial is going on I think it would have scared me. You know, oh my god, those terrible things could go wrong with me." [08 A/N def yes]

The Magpie Trial provided posters to be displayed throughout the hospitals. Most women could not recall seeing the posters; one woman who did, and evidently read the poster and therefore aware of the Magpie Trial, still did not fully appreciate she could be eligible:

"Well it was first mentioned when I was actually in the delivery room but before then I was in the waiting area waiting to go in and I actually spotted a poster on the wall and read about it and I remember thinking well that doesn't apply to me, I thought that you couldn't get pre-eclampsia at my stage of pregnancy, at the end. I assumed it was something that you got at 20-30 weeks pregnant and so I was in the labour room and they had started me off and I was catheterised and they were taking my blood pressure and the midwife mentioned to me about the Magpie trial and I did say 'oh I have just read a poster about it'." [37 P/N def yes]

6.3 Women's understanding of the Magpie Trial

6.3.1 Purpose of the Magpie Trial

The women were directly asked in the interview what they understood to be the main aim of the Magpie Trial. All the women responded to this question; however, there was evidence of varying degrees of understanding and recall. The women's responses as to why the trial was carried out were assessed against three key points described in the trial information leaflet:

1. Prevent an eclamptic convulsion
2. Help symptoms of pre-eclampsia
3. Benefit to the baby

Although all three points were considered components of a good understanding of the purpose of the trial, prevention of an eclamptic convulsion was the overall main aim and therefore considered the most important of the three points.

Most women held a combination of views regarding the main purpose of the Magpie Trial. Fourteen women correctly stated it was to prevent an eclamptic convulsion; the most common (n=26) understanding of the purpose of the trial was that it was connected with alleviating the symptoms of pre-eclampsia. Thirteen women appreciated there could be benefit for their unborn baby also. Nine women reported the main aim of the trial was to lower raised blood pressure, which is one of the main symptoms of pre-eclampsia. However, magnesium sulphate was being used as a prophylactic anticonvulsant. Although it is used as an antihypertensive in the United States, there is no evidence from randomised controlled trials to support this; and it was not used in this way in the UK, for which reason lowering of the blood pressure was not mentioned in the trial information leaflet. The following quotes illustrate how some women held a combination of views regarding the purpose:

> "It was trying to find out whether magnesium sulphate does help in pre-eclampsia, whether it does stop convulsions, before it escalates into eclampsia, because it can be fatal" [30 A/N prob yes]

> "She [*the midwife*] told me that it will stop you stroking or fitting during and after labour. That is basically what she said." [06 A/N def yes]

> "As far as I remember it was just sort of a brief. It is a trial they are doing to see if it helps people with pre-eclampsia to stop them from having fits – that sort of thing." [05 A/N def yes]

"My understanding was at the time you were trying to find out if magnesium sulphate would alleviate the symptoms of pre-eclampsia and HELLP *[Haemolysis, Elevated Liver enzymes and Low Platelets]*. It would bring my blood pressure down stop me from having a fit, a seizure". [03 A/N prob yes]

"I thought it was carried out to see if there was a way you could lower the blood pressure while in labour by testing drugs and using a study group, split the groups into two. Half would get the drug to lower blood pressure and see how effective that was through labour." [29 A/N not answered]

However, other women had less of a clear understanding of the trial aims:

"They just told [*partner*] they were going to have to give me some drugs to help me, otherwise I could deteriorate they said." [33 A/N def yes]

"I thought after what I had been through I will take part. To be honest with you I didn't really know what I was taking part in, I didn't have a full understanding". [19 P/N def yes]

"If I understood it was about pre-eclampsia then I would have understood it was about fits, but at the time I didn't". [27 A/N prob yes]

6.3.2 Implications of joining the Magpie Trial

Altruism and personal benefit:

There was considerable consensus among the women that there were benefits to be gained from joining Magpie. Most women (n=25) mentioned altruism and wanting to help future women in a similar situation as a key motive for and benefit to joining:

"It was nice to see, no matter what I was given I had helped in something good and that makes you feel good and no one can give you that. No one can take that away from me, I have helped in that and if someone else goes into hospital now with pre-eclampsia, feeling the way I felt they can be helped. It was from me joining. Not me on my own, thousands of women in labour but I have helped and this makes you feel good, it makes you feel good about yourself." [39 A/N prob yes]

"Well I appreciate that pre-eclampsia is a serious condition for lots and lots of women in all different stages of pregnancy and I just thought that if people volunteered to go on a trial that they could help people in the future so I could just do a little bit for the community really. I appreciate that if I didn't take the drug then I am not doing any good at all but if I had taken the drug and it had proved wonders then at least we are doing a little bit." [07 A/N def yes]

"To be perfectly honest I was more than willing to be involved. If it was going to prevent another person going through what I was going through with each pregnancy, I thought it has to be worthwhile, so I was more than happy to go into the trial." (28 P/N prob yes)

However, it was apparent that only a minority (5) of women identified altruism exclusively as the reason for taking part. The majority (20), talked about helping others in conjunction with perceived benefits to themselves and their future children:

"I just remember thinking it sounded like a good thing to sign up to do and plus if you can be of any help to people in the future in the same situation that it wouldn't do me any harm and something I was interested in doing. I suppose I thought it would stop it getting any worse and if it stops it getting any worse it would stop it harming the baby in the same way. Obviously, if my blood pressure was getting higher and the protein was increasing, he was getting less nourishment and I thought it would help him as well as me, in that respect." [04 A/N prob no]

"I suppose you live for the moment and the moment was this may help me and I don't think I pondered on it too much. There was two things there, one it was going to benefit me two it was actually going to benefit a lot of other people." [13 A/N def yes]

"I think I purely took part because I had had high blood pressure with first baby and it was the fact that everyone kept saying it is quite rare to get a second time, and as severe as you have it this second time. My mum had it with me, my sister and my brother and I was thinking well it obviously runs in

> the family and it is obviously something that needs looking into. That was one of the main reasons for taking part in it. I knew that I had my two children now. I was not having any more. It was not going to help me, but it would help women in the future, that is why" [19 P/N def yes]
>
> "The fact that if I joined and the research was done then it can only help later on, suggesting that if I was having a baby and she was a girl it might happen to her or even my sister. The research would obviously be helpful for them, for other women too." [06 A/N def yes]

Altruism and personal benefit have been identified by many as the most frequently given reasons for wanting to take part in a trial (Edwards et al 1998, Baren et al 1999, Welton et al 1999, Ellis et al 2001, Madsen et al 2002, Canvin and Jacoby 2006). Two of these studies (Baren 1999, Canvin and Jacoby 2006), are particularly applicable to the QUOTE study, as both explored consent to a drug trial. Baren et al (1999) elicited the opinions of parents whose children were being seen for minor traumatic injuries in an emergency department. Parents were surveyed to find out their reaction to a proposed drug trial for childhood seizures. Sixty-six percent (149/227) of the parents stated they would give consent for their child's participation. Among the consenting parents benefit to their child was cited by most (85%), then benefits to other children (72%), and to further medical knowledge (60%).

Canvin and Jacoby (2006) in their interview study also explored why patients might and might not take part in epilepsy drug trials. Of the 19 participants interviewed who had agreed to participate in SANAD, a trial comparing standard with new drugs for epilepsy none agreed for purely altruistic reasons alone; personal desire and self-interest were also key to participating.

Additional monitoring:

Similar to the findings of others (Mattson et al 1985; Welton et al 1999; Grunfeld et al 2002), receiving increased monitoring and surveillance by clinical staff as a result of joining the trial was also acknowledged as a

motivation in many of the women's accounts. Women perceived the surveillance they received as additional and therefore as ultimately guaranteeing better care:

> "So I thought it cannot do any harm, plus the more people that are doing checks on you the more, I thought the more I would be kept an eye on I suppose. I did get more checks. He [*obstetrician*] said we are really pleased that you have agreed to go on the Magpie Trial, I remember him saying even if you did not get magnesium sulphate at least you have been closely monitored and your condition has been watched." [03 A/N prob yes]

> "The nice thing about it was that the midwife stopped with us all the time and that was the thing because as part of the trial the midwife has to stop with you." [07 A/N prob yes]

> "I suppose you get a bit of extra care on top which is part of the job, I mean a bit more care and attention. Yes I think perhaps because I was part of it [*Magpie Trial*] they were perhaps more open about things and willing to talk to me. Because they needed to gain information for the trial then I got obviously more regular checks, maybe not more regular checks but a bit more one to one for being part of it." [06 A/N def yes]

Additional information:

It is advocated that potential trial participants will need information about their diagnosis, the nature of their condition, and the treatments available before considering entering a trial (Wager et al 1995, WMA 2004, Canvin and Jacoby 2006, NRES 2008). In the QUOTE Study it appeared from the women's accounts of the consent procedure that some of the recruiting clinicians did enter into discussion regarding the diagnosis and treatment of pre-eclampsia in order to explain the trial. Additional information about their condition was usually in the form of discussion with the clinicians, but also from the trialists after recruitment as part of the follow up study. It was apparent that the supplementary oral information provided them with additional information on pre-eclampsia that they had not previously known. Women perceived that had they not been in the Magpie Trial, they would not

have been provided with this oral information about their condition, and that it was not part of usual routine care:

> "It has given me a lot of information about pre-eclampsia that I would not have had if I had not have been on the trial." [27 A/N prob yes]

> "It was quite informative *[being told about Magpie Trial]* and it was nice to understand a little bit more. They were very clear. I think I have certainly learnt a lot more since the trial and it was certainly helpful talking to you [RS] on the telephone and that was really in-depth." [13 A/N def yes]

> "I think perhaps because I was part of it they were perhaps more open about things and willing to talk to me. Because they needed to gain information for the trial then I got obviously more regular checks, maybe not more regular checks but a bit more one to one for being part of it." [06 A/N def yes]

> "I think it has benefited me in the fact that I am more aware of pre-eclampsia and the symptoms and what it can do to me. I think probably because I have my circle of friends who know I am involved with the trial and I can talk to them about pre-eclampsia symptoms. I think the fact that I joined the trial made me more aware of pre-eclampsia and I think if I had not had that conversation with the girl *[midwife]* I would probably have known next to nothing. So it has made me more aware. I think it has benefited me in the fact that I am more aware of pre-eclampsia and the symptoms and what it can do to me." [08 A/N def yes]

6.3.3 Appreciation of possible risks of joining

Potential hazards of magnesium sulphate are related to smooth muscle relaxation and include respiratory depression, hypotonia and hypotension (British National Formulary 2008:508). In the USA magnesium sulphate is also used for tocolysis of preterm labour, although in much higher doses and for a longer duration than when used for pre-eclampsia. There has been considerable controversy about whether *in utero* exposure to magnesium sulphate, rather than other tocolytic agents, for the prevention of preterm birth, increases the risk of mortality for the baby (Mittendorf et al 1997). However magnesium sulphate also has the potential for benefit. For

example, magnesium sulphate may reduce the risk of eclampsia, and its complications, such as renal failure, cerebrovascular accident and liver failure, as well as improve blood pressure control (Belfort and Moise 1992). These benefits may be reflected in a reduction in preterm delivery, and lower risk of cerebral haemorrhage and cerebral palsy for the children. The Magpie Trial was evaluating magnesium sulphate on such outcomes.

The Magpie Trial information leaflet (Appendix 16) stated the following regarding possible risks to the women:

> *"Very rarely if too much magnesium sulphate is given it can cause a temporary muscle weakness, which can lead to breathing problems. To stop this happening reflexes and breathing rate are checked regularly. Sometimes there are side effects of magnesium sulphate. These can include nausea and vomiting, thirst, drowsiness and confusion, but they all disappear when treatment is stopped." (Magpie Trial Information Leaflet 1998)*

And to the baby:

> *"Magnesium sulphate may help the woman's kidneys to work better and may help prevent the baby from being born too early. There is very little useful research into whether magnesium sulphate really is the best treatment. Although one study has suggested that it might be good for women, this was not conclusive and gave little information about the effects for the baby." (Magpie Trial Information Leaflet 1998)*

Women that were recruited antenatally (n=29) were specifically asked in the interviews about their thoughts regarding the possible risk to their unborn baby. There was overwhelming consensus among the women that joining the trial was not associated with any harm or risk to either themselves or their unborn baby. It was apparent their understanding regarding harm came from information received from the recruiting clinician by whom they were given reassurance:

"I think I asked if there was any risk to children, because obviously I would not put them at risk, she [*midwife*] just said 'none'." [34 P/N prob no]

"They told me it was completely safe and there was no harm to the baby or me and no long-term damage and that's how I felt about it." [16 A/N def yes]

"I felt fine about it. I remember being told if I did get the drug it would have no ill effects on me or the birth or baby. I think I remember seeking those kind of assurances. But no it did not bother me." [08 A/N def yes]
"Well, I wasn't concerned because they settled all my worries down once I asked them questions anyway - the main question was it is going to harm me or me kids and they said no - so it was ok." [22 A/N def yes]

Some women recalled asking about the possibility of side effects of the trial treatment. From their description of the information they received, it appeared to be understandable and reassuring; and for some, it seemed to guarantee the safety of the trial and make it straightforward to participate:

"I asked her where there any side-effects and she said there was a slight risk if you did receive the magnesium sulphate that you would be more sickly." [37 P/N def yes]

"There were not any risks to me but I could suffer nausea. That was the main thing and I remember saying 'god, I have had nearly eight months of sickness I don't want any more'. Dizziness I think was one of them as well. I cannot remember any more. There was a list, but I can only remember them two." [11 P/N def yes]

"They did explain all what it could do for me. There were very minor side effects and I agreed straightaway." [17 P/N prob yes]

Some women had just not considered the possibility of harm at all to either themselves or their child:

"I did not think of it. I did not see what much more harm could have happened because I was so sick anyway. I was under the impression that it

was ok, nothing particularly dangerous, it was quite safe. It was a harmless substance they were giving me, not that it would work or would not, but it would not do me any harm. They were not giving me poison." [31 A/N def yes]

"It didn't get discussed and to be perfectly honest I never even thought about it myself because your mind is elsewhere I never thought about it. Well yes obviously if it is going through my bloodstream then the baby is going to get it as well isn't it? But I never thought about it at the time to be quite honest." [07 A/N prob yes]

Others did worry about potential risks to themselves and their baby. There was evidence of calculating the level of risk associated with the trial intervention and pre-eclampsia:

"Then you have to weigh up also if you do fit, then that obviously has an effect on your baby too. It is kind of how close am I to having a fit? Is that going to be more damaging to my baby than going on the trial. So it is a tough one really. I think under the circumstances, the fact that I was likely to fit was quite real, that probably would have been enough to make me think that it was worthwhile. At the end of the day, hopefully those chances are minimal compared with the chance of me fitting. " [09 A/N prob yes]

"As in a risk to me? No it was not explained that there would be a risk, you could have an adverse effect, but you can with any drug, it is the risk you take and you take it because you want to. I was under the impression and I still am that the amount I was given before I had the baby it would not have got enough into him to have any effect. It could not be proven that there would not be nothing at all that he would not get any of the drug if it was the drug. For what he would get, the benefits would far outweigh that. It was like you take the risk. I asked about the baby, but I think at the time you are not bothered about yourself. I was only bothered about the baby so I did not ask about myself." [39 A/N prob yes]

"Because it's not in my mind I think I put to bed that there would be a risk or at the end of the day if I get the placebo then it's nothing and if it was

magnesium sulphate then obviously, the research that's happening now, and I suppose there is always a percentage of things, there could be side effects in years to come but I suppose you live for the moment and the moment was this may help me and I don't think I pondered on it too much. There was two things there, one it was going to benefit me two it was actually going to benefit a lot of other people. I think it's fair to say if they had said we don't know how this is going to affect your baby at all there could be serious consequences then I wouldn't. But I can't ever recall being told that or having that understanding so in my own mind I thought it's minimum risk to myself now and in the future. It's something I'm going to do for now, that was the situation at the time." [13 A/N def yes]

It was evident some women felt their life was at risk and joining the Magpie Trial was their only hope of recovery:

"I think they had decided that I was by that stage so ill I needed it. Or it was a case of obviously they did not know whether I would get it or not, but they thought let's try it. A case of trying anything because they were trying to get me stabilised before I could go for surgery. I think the doctor was very concerned so he said he thought it would be a good idea, and obviously you have got to trust your doctor which I did, I thought he was very good. I think if they said to me 'you are in a life or death situation we have run out of ideas.' I seem to think they had done everything they could with me and the only thing was the magnesium sulphate and deliver the baby. I think you are at that stage and they say to you 'the benefits far outweigh the risks'. "[03 A/N prob yes]

"Apart from it might help the blood pressure in some respects but at the time really apart from the conventional way of dealing with it I don't think they had much option." [26 P/N def yes]

"All I thought at the time was from what the doctors were saying to me and what the paediatrician was saying about the baby, I felt like I had all the odds stacked against me anyway and I did not have anything to lose by going into a trial. If it was going to help me, if there was anything that was going to help

me it was worth trying. So I was more than happy to go into the trial." [28 P/N prob yes]

For some, the possible detrimental effects for the baby were secondary to their own survival; including one woman who was aware that there was little hope for their baby's survival:

"We knew the baby was small and to be honest we did not think there was much hope for the baby being small, they had given us an idea and we knew the lungs would not be developed and what have you. But then again it did not say that there was any harmful effect, just that nothing was known." [32 A/N not sure]

"But then at the time, you think well we could both die, your focus is on living as opposed to if there is a minor chance that it could have some effect on the child." [09 A/N prob yes]

Some women had actively discussed the issue of their own survival and that of their child's:

"I have the view that, and I used to say to my husband, if my health is at risk I come first and if it was going to that I already have a daughter at home and to us my health was more important. It sounds awful doesn't it - very cold but to me if it was going to prevent me from being ill what use is another two babies and no mother? I always had that view that if it was going to be either me, or the babies it was going to be me that was saved." [37 P/N def yes]

In summary, several issues emerge here about the women's knowledge of risk. First, many knew nothing about risks and made no assumptions about them. Second, many more believed no risks were present. Some seemed to have assumed this, but the majority said that this was what they had been told. Third, relatively few recognised the possibility of unknown risk, and it was not clear whether they had been informed of this possibility. It is possible the women may have translated the statement in the trial information leaflet reporting that one trial suggested that magnesium sulphate might be good for

women (but gave little information regarding the effects on the baby) as meaning 'no risk'. The perception of risk to some extent is situational and therefore complicated for those participating in the Magpie Trial. Most of the women were experiencing severe pre-eclampsia, and the Magpie Trial may have been viewed as their final hope of worthwhile treatment.

6.3.4 Mixing clinical care with the Magpie Trial

The women were recruited at a time when they were likely to be having intensive monitoring: restriction of oral fluids, blood pressure checked every 15-30 minutes, tendon reflexes checked hourly, and the urine measured hourly, insertion of urinary catheter and intravenous infusion. Care that was connected exclusively to the Magpie Trial was an extra intravenous line and frequent discreet observation of the respiratory rate. However, many of the women appeared to have difficulty separating aspects of the Magpie Trial with that of standard care:

> "I had to have the catheter in for the trial and that wasn't very nice at all and the drip wasn't nice either but because I couldn't move around anyway because I was wired up to monitors then the drip wasn't much of a problem. I don't know if the catheter was there because of the trial. I would have said no because the catheter was horrible I have never had a catheter in before but I know people who have and it was just horrible and you couldn't drink or anything and I was dying for a drink. I couldn't have a cup of tea because they were monitoring me." [29 A/N not answered]

> "The only thing, I don't know whether, you know you weren't allowed to drink, you were only allowed a certain amount each hour." [23 P/N def yes]

> "They came to me every half hour and gave me a small egg cup it seemed of water. I cannot remember whether it was before or after and I remember thinking I wonder if this is for the Magpie Trial? Or because of my condition. I remember thinking I wonder why they are doing this? I wonder if it is to do with the Magpie. I remember they were measuring my intake and my out-take." [03 A/N prob yes]

"They explained it was just a drip and never said it was two drips. So I couldn't move off the bed. I couldn't go the toilet so I had to have a catheter on and I felt as if I couldn't move. Other than that the only thing was the next day it had to be on for 24 hours. I couldn't actually move from the bed until 24 hours after. I wanted to get back on the ward and walk about." [15 A/N prob no]

Sometime intensive monitoring meant being too ill to care for the baby:

"They said then I would be checked over the next 24-hours and stay on a machine, sort of thing. That was probably the only one regret that I have, that being my first and not knowing I let them take him off me for the first night. He just went up to the ward and when I went up the next day he was jaundiced with being three weeks early, and ended up on a 'Billy blanket' and so I didn't really get to bond with him as quickly as I probably would have done. That's the only thing I regret about it I wouldn't let them take the baby away again." [12 A/N def yes]

"I remember thinking. Well I have not been told this! I did not realise that she would be taken away and I would go into another room in the high dependency unit and I did not expect that. "[06 A/N def yes]

6.4 Women's understanding of methodological principles of randomised trials

6.4.1 Random allocation

Almost all the women were aware of at least one concept relating to random allocation, although their explanations often suggested an unclear understanding. The responses implied that the concept of randomisation was not discussed in any great detail by the recruiting clinician. Most women described random allocation as meaning that their clinician or hospital did not know which treatment they would get:

"I don't honestly know, it's just random isn't it? Basically they just pick, some they do, some they don't, so some get one, and some don't" [18 A/N def yes]

I have no idea, but my opinion is, well what I assume happened is that the hospital get given a whole load of whatever it is and that the hospital should not know what it is and they just pick one and give it to you, and that they have no idea of what they are giving you or not giving you and I assume that is what happened." [09 A/N prob yes]

For those women that had a clearer understanding of randomisation terms used were 'pick out of a hat', ' the next box of the pile' (referring to the Magpie Trial treatment packs), 'a 50-50 chance':

"It [*randomisation*] did not necessarily mean that the next person would be given the real one. I understood it was just like pick out of a hat. Some women on the drug and some women not on the drug." [39 A/N prob yes]

"I think it was just get the next box off the pile and that was it. I took it that you *[clinicians]* put your hand in a box and it was what came out. I did not know whether, and I would take it that everything is blind because they cannot say get the box of placebo or magnesium sulphate. I just thought every package was the same and they *[clinicians]* did not know either, they were not thinking this person's blood pressure is higher, I did not take it to be that." [14 A/N def yes]

"My understanding was that it wasn't chosen, my understanding was that they were kept in the fridge in a big pot marked 'Magpie Trial' *[and]* depending on which one they took it was either the placebo or the magnesium sulphate." [13 A/N def yes]

One woman understood from information given by the staff that the trial treatment was allocated consecutively:

"I think it was the nurse in the delivery suite not the sister who put it to me initially. It must have been after I had the reaction when they started and she just made a passing comment that 'well we know you have got it and next door hasn't' Because the woman in the next delivery suite to me, she must of had A and I had B or vice versa. So with me having the reaction she said: "we can presume she had the saline." [40 A/N prob no]

Two women considered the term 'randomisation' not as a method by which study participants are allocated to receive one of two (or more) treatments, but as meaning that they themselves as individuals would be selected at 'random' by the clinicians to participate in the trial:

> "I think they said the mums would be randomly selected, I'm not sure really, I can't really remember if they [*clinicians*] said not everyone who has high blood pressure was being monitored. I think it means a selection of people it doesn't matter, not an ethnic group, just a random selection of people, no age limit, that's what I think it is." [29 A/N not answered]

Women were asked how acceptable randomisation was within the confines of a trial:

> "Not so bad I suppose. Everybody was in the same position." [06 A/N def yes]

> "I think it should be random. If it was the other way around then I do not think the trial should have existed. People would just say 'give me the drug!' No if you don't know, to get the best result from the study you have got to randomise it. You cannot say everyone with the highest blood pressure and protein in their urine etc would get the drug and anyone who is a bit less, because then obviously your figures would not tally." [14 A/N def yes]

Others, however, were less convinced about its benefits:

> "It made me worried then because I thought 'oh no maybe I will need the magnesium sulphate'. I know I asked the nurse well if you think magnesium sulphate will help, can you not give it to me anyway?' I asked that because I thought what happens if I am getting the blank one and I should be getting magnesium sulphate and she explained to me that is how they did it." [03 A/N prob yes]

6.4.2 Equipoise

The concept of equipoise, as previously discussed (Chapter 2:56), was important to explore with the women, as randomised controlled trials should only be carried out when the effects of an intervention are unclear. The accounts provided by most of the women suggested that they understood that the aim of the trial was to assess the value of magnesium sulphate in preventing eclampsia; but little mention was made of the concept of equipoise when they described the trial. Their descriptions regarding understanding of the concept of equipoise suggested that some women perceived that their clinician was not actually in clinical equipoise regarding the benefits of magnesium sulphate.

Several women indicated that clinicians already had a strong preference for magnesium sulphate as a drug that would prevent them from convulsing. This is not surprising, given already available evidence that it did (the main objective of the Magpie Trial was to assess whether any benefit was overall and worthwhile). Based on the interviews, however, it seems that clinicians did not discuss equipoise either in the general sense (i.e. the uncertainty amongst experts in the field) or in terms of personal equipoise (i.e. that they themselves were in equipoise regarding the effectiveness of the trial treatment). In fact the women's accounts suggest that many clinicians had clear treatment preferences, in favour of magnesium sulphate. Moreover the women, believing the Magpie Trial offered them the best treatment as promoted by the clinicians, were influenced more positively to join the trial. The women appeared reassured about the trial, talking about the fact that the clinicians were experts in pre-eclampsia; and therefore they gave their trust to the clinicians' clinical ability to advise them:

> "Well obviously it was not put over to me that it was only of benefit, because I could have had the placebo, but basically it was kind of put over to me that the magnesium sulphate, if I did have the magnesium sulphate then in their opinion that would be of benefit. What actually struck me at the time was if it is of benefit why are they not giving it me anyway. " [09 A/N prob yes]

"I suppose when you are in a profession that you know a lot about you have a good idea that something probably is [*beneficial*]. I get the impression that you have an idea, obviously you have an idea because that is why you do the trial. I think they all had an idea and that they wanted it *[magnesium sulphate]* to work, and that they thought it did and obviously doctors want the best for the patients, don't they?" [03 A/N prob yes]

It was evident that clinicians discussed with the women the use of magnesium sulphate in other parts of the world, thus giving further reassurance of its safety and benefit:

"He came in to me on the HDU and he basically said you do realise you have had pre-eclampsia and then he was talking to the midwife so he was talking to both of us at the same time and he was saying it is not too late to do this study and has she been told about the Magpie Trial? I said no I have not been told about the Magpie Trial, what exactly is it? He was saying that he had worked in Africa, in every other country bar this one they give magnesium sulphate to pre-eclamptic women and for some reason this country will not believe that it does help to stop pre-eclampsia so if you would not mind would you take part in the trial or words to that effect. I cannot remember everything, but words to that effect." [11 P/N def yes]

"I didn't feel that it was any danger, the drug, because it was obviously being used routinely in America anyway and in my experience to get anything past the FDA [*Food and Drug Agency*] they can be far stricter than we are over here so I didn't feel a total guinea pig for a drug that was completely new on the market and you were completely going into the unknown there was a security there that it had been used before in a developed country so there was that security side to it. That was obviously reassuring going into it and whether if you hadn't have had that I wouldn't have done it I don't know really. But that was definitely was a pull I was confident that there was going to be no surprises if you like." [37 P/N def yes]

"At the time of joining, when it was explained to me, when the midwife explained to me it was explained in a way, that if I was given the correct drug and not the placebo, it would stabilise me. I understood the benefits to the

> baby, if I was given the right drug it would bring my blood pressure down so it would have to help the baby." [39 A/N prob yes]

6.4.3 Use of a placebo

All women apart from two understood that they were either administered an active drug or a placebo as part of the Magpie Trial. One woman had no recollection of joining the trial at the time; in fact, she was informed some days later that her husband had agreed to the Magpie Trial on her behalf. It is likely that this woman had imminent eclampsia and that her husband had understood she would receive a drug to help:

> "They [*clinicians*] just said she is extremely ill, she needs it for life. So it scared him. [*husband*] did not know what he was signing for, he just knew he had to sign for this medication." [33 A/N def yes]

Another woman had no recollection she had joined a research trial, she assumed she had consented to a treatment:

> "To be honest with you I didn't understand it was research, it was quick, and it wasn't lets think about it. I didn't realise it was research until Rebecca came out to see myself and the baby I didn't realise it was research until then. I didn't realise that at all because I was under the impression that I did have that drug, when I signed the form I assumed I was signing for that drug." [25 A/N prob yes]

When describing the comparison arm of the trial the women often used the word 'placebo', which was how the inactive treatment was described in the Magpie Trial information leaflet. Other terms used by the women were: "a harmless solution", "a dummy", "the blank one" (refereeing to the treatment pack), "water injection", "saline", or not the drug". To describe the active treatment the women often used the correct name for the drug, (magnesium sulphate), as named in the trial information leaflet. Other terms used by the women were: "the actual thing", "the real one", "the correct drug", and "the real stuff". It was evident from the women's descriptions of events they were

quoting back terms used by the clinicians to describe the trial; and that their vocabulary was informed by the way the clinicians chose to phrase how the trial was designed:

> "She [midwife] just told me I would get the magnesium sulphate or I could get like water, a harmless solution, I didn't know what you would call it." [03 A/N prob yes]

> "They [*clinicians*] said they would either inject a certain drug or [*it*] could be water." [23 P/N def yes]

> "If I remember rightly, I was on the labour ward and the lady [*clinician*] came in and asked, and told me about the Magpie Trial. She said it was about the real stuff and the placebo and would I take part in it" [18 A/N def yes]

> "She [*the midwife*] told me that it was a case of during like the labour either the placebo or magnesium sulphate, one or the other, they don't know what it is, so it may control your blood pressure. She said you might have the placebo or you might not." [06 A/N def yes]

> "They said that it was to do with being put on a drip and some people would get something to lower the blood pressure and some people would just get water and they wouldn't know which was which and they put me on a drip." [29 A/N not answered]

Some of the women recalled what the probability was of being randomised either magnesium sulphate or placebo:

> "I understood that I had a 50:50 chance of having one or the other." [04 A/N prob no]

> "Half got the drug half did not get the drug." [31 A/N def yes]

> "I just thought I have a one in two chance so it was a good chance and felt ok about that actually." [16 A/N def yes]

The women were asked how they felt knowing there was a possibility they might receive a placebo. Most had no concerns:

> "They also explained that I might not get the drug it could be something completely different and they explained to me why they don't know which is the drug and which isn't. I mean I was a bit apprehensive but they explained to me you could get water or... it would be nothing to harm you or the baby so that put my mind at rest it was just when she said it might not be the drug I thought well what are they giving me? I was more concerned about the baby but they were really understanding." [36 A/N def yes]
> "I knew that it would only be saline anyway, so if I got it, it wouldn't harm me anyway." [40 A/N prob no]

> "It made me worried then because, I thought, oh no, maybe I will need the magnesium sulphate. I know I asked the nurse well if you think magnesium sulphate will help can you not give it to me anyway. I asked that because I thought what happens if I am getting the blank one and I should be getting magnesium sulphate and she explained to me that is how they did it." [03 A/N prob yes]

For others the implications of being randomised placebo were negative. For example, women expressed concern about what the solution was made of and how their body would react to it:

> "The only thing I was worried about was the placebo. I mean what was it? I did have to ask and would that harm if you know what I mean. I was reassured it wouldn't. I cannot remember what it was now". [06 A/N def yes]

> "I did worry about whether I did have the placebo, how long would it take you to realise that I had, and would that have an affect on me?" [32 A/N not sure]

One woman described her situation following the birth of her baby and the impact on her of possibly being randomised to placebo:

> "The doctor who came said you can tell she is on the placebo, I felt gutted really, she was looking at something or other. I don't know whether it was my

> blood pressure reading or not or some other reading, because I had so many different readings. But I just remember her coming along, having a look and saying she is obviously on the placebo or otherwise this would be somewhere or that would be somewhere, some figure would be different, and that was all I remember about that really. I did find that intensely irritating really, because I had this extra, I had so many tubes in me and I was in the high dependency unit and I had, they were trying to get me to feed my baby and I had all these flaming tubes coming out of everywhere getting all entangled and she *[the baby]* was trying to pull them out, and I had this extra one for the trial. At that time I kind of felt if the doctor knows I am on a placebo what is the point of having a placebo if the doctor knows. What is the point basically, that is how I felt" [09 A/N prob yes]

In exploring this further in the interviews, it became apparent that some of the women appreciated, at least in part, how the trial was designed: that in the event of them subsequently having an eclamptic convulsion whilst on the trial treatment (whether active or placebo), the trial protocol dictated they should be given magnesium sulphate (i.e. emergency care was to give a bolus of magnesium sulphate immediately to control the convulsion). This emergency treatment was not actually described in the trial information leaflet given to the women, but clinicians were provided with instructions in the Magpie Trial protocol, should the situation occur. Thus, women's understanding of this aspect of the trial came from the oral information given to them by the recruiting clinician. This understanding resulted in women being reassured about the safety of the trial and may even have been key to them joining. The women talked about the fact that being randomised to placebo would not disadvantage them in any way, since had they had an eclamptic fit they would have been administered magnesium sulphate:

> "I think also the fact that they were going to give you *[magnesium sulphate]* if you had a fit, even if you were on the placebo. You've nothing to lose really did you by going on the trial? Because: a) if you didn't have a fit then great b) if you did have a fit then you were going to get magnesium sulphate anyway." [37 P/N def yes]

"I was not worried about *[convulsing]* because I was told the study would be stopped and I would be given magnesium sulphate straight away, to give it to you when you start convulsing and it was the study that was actually giving it as a treatment. I did not feel I was put in any danger." [27 A/N prob yes]

"I felt that if anything did start going wrong, if I did start fitting then if it was a placebo they would have used magnesium sulphate anyway. So I did not think there was any greater risk in taking part in it to not taking part in it." [01 A/N def yes]

However, the women only described this scenario when contemplating the possibility of being randomised to placebo. None of them appeared to appreciate the difficulty they could have been in had they been randomised magnesium sulphate and then been 'over treated' with magnesium sulphate (risking toxicity) to control a convulsion.

6.4.4 Treatment blinding

Many women, especially when talking about the trial being placebo controlled, made explicit reference to the use of blinding, both of themselves and clinicians and why this method is necessary in such a trial:

"I understand that there was a lot of women taking part and half would be given magnesium sulphate injections and half would be given another injection and nobody, not even the doctors knew which one they were given, so to enhance the trial nobody knew what they were given" [30 A/N prob yes]

"Well they have got to be in the same position as the patient haven't they? If they knew that it was just the saline, then they would be treating you differently than if it was the magnesium sulphate, so it is best that they don't know that they just say it's one or other and then it makes it fairer" [05 A/N def yes]

"She *[doctor]* said that there were two types of bottles which we could get, saline, and whatever the other test was. We would not know what we were getting and the midwife who was giving it would not know" [34 P/N prob no]

"Yes, I suppose if people do know what they are on, it might affect how they behave or their thoughts. Stress, things like that might come into it. You have not got something to control so you have got to be in exactly the same situation as someone who had got magnesium sulphate, and if you did know what you were on, it might affect. Probably stress thing is the worry, or you might be treated differently by the staff. They might monitor you more or something like that, so it's not a proper trial or evaluation, they are not equal" [01 A/N def yes]

Difficulties associated with blinding, especially when using a drug that has obvious known side effects were also recognised. The women indicated in the interviews that clinicians could figure out and even intentionally try to guess what the treatment allocation was:

"[*The midwife*] did actually say that although we're not supposed to know I will know from how you react whether you have received the magnesium sulphate, but that was just her comment, from her experience" [37 P/N def yes]

"I vaguely remember the doctor saying when we were there and it was uncomfortable going in, I just remember the doctor saying 'well I think you have got the drug'. I remember thinking, I don't think you are supposed to tell me that" [19 P/N def yes]

"I remember them saying it is supposed to be a blind trial, however, they felt that they could tell the difference between the liquids going in, that was what was said at the time. But they did not say 'oh you have received a placebo or something like that'" [14 A/N def yes]

"Somebody was asking if I was getting any sensation and I told them what it was. I remember them writing that on a form, I was convinced I had it, I felt like and they were thinking she must have had it. I was getting strong signals, it was obvious the staff knew" [31 A/N def yes]

6.4.5 Thoughts on treatment allocation

When the women were asked to guess, as part of the interview, what trial treatment they thought they had been allocated to, just over a quarter (11/40) said they did not know. Twenty-two (55%) were correct about their treatment allocation, of whom 17 had been randomised magnesium sulphate:

	Randomised magnesium sulphate (n = 22)	Randomised placebo (n = 18)
Guessed magnesium sulphate	17	5
Guessed placebo	2	5
No idea	3	8

Table 6.1 Thoughts on treatment allocation

Some women expressed a clear treatment preference at the time of recruitment, the most wanting magnesium sulphate, because they believed it to be the most effective treatment:

> "It must have been after I had the reaction when they started and she [*midwife*] just made a passing comment that "well we know you have got it [*magnesium sulphate*] and [*woman*] next door hasn't. So with me having the reaction she said we can presume she had the saline. I think it just stopped the curiosity of thinking whether I actually had it or not. So at least I know I have had it, at least I've got it so it is lessening the risks to the baby. I was getting an extra treatment that the woman in the next room wasn't getting" [40 A/N prob no]

> "As soon as they put the drug in - I felt a pain in my arm, like a numbing pain and it was like shooting pain in my arm and it felt numb at the time. It was painful but it was only short pain. I understood that I did have it now, but I had an idea that I did. I'm glad actually. I think it made my pregnancy easier." [16 A/N def yes]

When asked to consider how she would feel if randomised a placebo one of the women said:

> "I suppose it would make me feel disappointed in a way. Because, I would want to prove that magnesium sulphate is of a benefit. I would think, oh what a shame. I don't mean it does not work just because it did not help me, but I feel so much like it did, I kind of want it to because I can say great it does work. I would be disappointed. I do intend to write and find out because I would be really interested to find out. I would be disappointed, I really would" [03 A/N prob yes]

Another held similar views:

> "I would be fuming. I have got the details to send for but I have not done it yet. I would be fuming. My baby is fine and I am fine, do you know what I am saying. I think my blood pressure took a while, so I believe in a way that I did not get it, because my blood pressure was too high. I came off the Magpie Trial at 11.00pm that night because I had had enough of being downstairs [*delivery suite*]. Not enough of the trial, I just wanted to be back upstairs and calm. It is all rushing around when you are in delivery suite. I would be like they could have given me the real one, why have they given me that? But then you have to do the trial and I understand someone has to do that, so it might as well be me" [39 A/N prob yes]

Other women described how they felt when considering they might have been randomised the placebo:

> "I do remember somebody saying that they thought I had it [*placebo*], which was not very nice to hear but then again I don't know whether they did know if I had it or not. I don't know really. They said that I had the placebo, because my blood pressure was not stabilising and I did not really know what was going on, but I remember hearing that. I wanted to shout out and I could not, you know to try and find out what was going on" [32 A/N not sure]

> "I think they thought I did not get it [*magnesium sulphate*] I can remember him [*doctor*] saying that. I think I would prefer that I did [*have magnesium*

sulphate], I think I was disappointed, I think that. Just another kind of precaution I suppose" [10 A/N prob no]

6.5 Conclusion

All of the women seemed able to recall the words used to describe Magpie and/or to understand at least some of the methodological principles underlying the trial design. Most of the women appreciated that randomised controlled trials involve the uncertainty principle, assign treatment allocation randomly, can involve blinding, and can be placebo controlled. The level and extent of knowledge varied between women, reflecting their particular experience and prior knowledge. The data presented in this chapter provide some insight into the women's experiences and understanding of the Magpie Trial. In interpreting their experiences it is important to appreciate their circumstances at the time. The main difficulties the women identified were related to the emergency situation they were in and the timing of the approach. They felt it was a confused and complicated time, leaving them not able to think clearly, yet requiring them to make important decisions in a relatively short space of time. In view of the difficulties around the time of recruitment, women's understanding of the Magpie Trial and their grasp of the methodology and study design was remarkably sophisticated.

Chapter 7

Women's views regarding the decision-making process

7.1 Introduction

This chapter presents the themes related to the process of decision-making. The decision-making process was a focal point of the interview schedule. Women were asked about several aspects of the decision, such as how difficult or easy the decision was to make, what considerations had to be made; for example their circumstances at the time, who was with them and what involvement these people played, including the recruiting clinician. Women were asked about the timing of approach and how quickly their decision was made, and whether advice was sought at the time of agreeing. Their views about the quality of the information received were also explored.

7.2. Making the decision

As with many emergency situations where treatment is needed urgently, women eligible for the Magpie Trial were required to make their decision to join in a very short space of time. Prolonged discussion could have meant delay to the start of treatment to the point where treatment became futile. For many women they had no prior knowledge of the trial and the short window of opportunity for a possible recruitment was problematic for some:

Speed of decision-making:

> "If I had been under different circumstances, I probably would have thought it through, but at the time you felt like you needed to make a fairly quick decision. I felt like time was not on my side. I think I made it within five or ten minutes. I did not think about it that much. " [09 A/N prob yes]

> "I did feel I was rushed then into making a decision about the trial, I had to consent, and I had all these forms shoved into me and I was not really sure what I was signing at the time." [32 A/N not sure]

"There was just a lot of commotion going on in the background. There was a lot of rushing around and 'we need to do this, we need to do that, she needs this injection', this drip going up, and then baby's cord was wrapped around his neck, so there was a lot of 'we need to get the baby out'. I was practically unconscious, but each time I opened my eyes there would be loads of people rushing around and getting things ready, so at the time it was just a quick decision and that was it, I did not think about it." [30 A/N prob yes]

However, for others their situations were different, and they described a much more relaxed and calmer situation. It appeared from their interviews that the decision to participate in Magpie was relatively easy and uncomplicated. This finding concurs with that of Snowdon and colleagues (2005), who interviewed 78 parents' to explore their pace of decision-making for one or more perinatal trials. The parents in Snowdon's study did not view their decision to enrol their unborn or newly born baby into a clinical trial as instantly problematic. Nor did some of the women in this study:

"She came and talked briefly to us about it and gave us some leaflets and then walked away and came back later. I said 'Yes'. It was quite a casual decision in a way. We didn't really agonise over it, as it seemed a sensible decision to be part of. It was quite an easy decision to make." [04 A/N prob no]

"When the midwife first mentioned it she gave us the leaflet to read and discuss and then she left us alone to talk about it ourselves and then she came back to see whether we wanted to take part. I can't remember sort of how long it was but I didn't feel pressurised in anyway. No, but even to participate to be fair, there was no pressure to sign up they did say it's completely up to you." [37 P/N def yes]

"In my own mind it was a very quick decision to make. It's fair to say they sold it to me or not sold it to me they told me about it. In my mind I had weighed up the pros and cons and decided yes, in probably minutes. Yes, I'm sure they left me alone and came back to me they didn't just say make the decision there and then. I must have read stuff about it and then they came back and I had no issues so, yes." [13 A/N def yes]

Questions on the interview schedule, however, contained an assumption that all women were in fact making conscious decisions. It was apparent that although they did understand they had taken part in a trial, they nevertheless seemed to have given only little thought or consideration to the decision to participate:

> "It was breeze really it didn't upset me and I didn't panic about it. I was more then willing to do the Magpie trial. It didn't bother me at all. I am quite interested in it anyway. It was quite informative and it was nice to understand a little bit more. They were very clear and I had no objections at all." [13 A/N def yes]

> "As far as I remember it was just like 'yeah whatever' sort of thing. I Knew what they were doing. I did not think at the time to ask if there were any side effects, is there this is there that? I just thought I will take part in it. I don't think I thought about it too in depth. It was not like 'oh well?' At the time it was like 'oh yeah I'll do that'. There was no major discussion of the in's and out's. Although we gave it thought it was not an in-depth discussion and what if, it was just we will take part." [09 A/N prob yes]

> "I did not really think about it, they could have asked me anything at the time and I would probably have said 'yes'." [30 A/N prob yes]

> "I cannot remember much about it, she was nice and did not put me under any pressure. I just said 'yes'" [31 A/N def yes]

Furthermore no one said the decision to participate in the Magpie Trial was "very difficult", only few gave it a "great deal of thought" and only two gave "serious thought of refusing". For most (n=34) their responses suggested their joining seemed straightforward in that they understood their involvement in the trial was reversible and that if, for whatever reason, they reconsidered it they were able to withdraw:

> "She did, yes, she said because I went for an epidural as well. She said "if you wanted to come out there is no problem," she said, "if you have got a lot on your mind or you have got other things to think about you can opt out no

problem". She was a very nice lass and she made everything perfectly clear." [07 A/N prob yes]

"They basically said if I remember correctly that an extra drip, but if at any point you feel you do not want to continue you can ask for it to be stopped. So I basically thought 'what have I got to lose', not in the best possible circumstances here anyway. I might as well go for it." [09 A/N prob yes]

"I knew it was a drip which you had for about 24 hours, any side effects, or it was not suiting me for any reason, I could come off. That is it really." [17 P/N prob yes]

7.3 Difficulty with asking questions

Asking questions at the time of recruitment appeared problematic for many of the women. In the main this related to the difficulty of their situation. Comments suggest the women were unclear or unaware of what was happening, or felt too sick and frightened to be concerned with what was happening. In some ways this is not unexpected given the stressful and unfamiliar circumstances for the women in which information about the trial was being offered:

"In a matter of seconds there were doctors and nurses around me that was very frightening and while they were doing, you know, putting needles in me, and so on no-one was really talking it was very silent and I was frightened to ask because you don't want hear the word, because my husband was there and he was upset, and you're frightened to say 'what's wrong?' just in case they say the 'baby hasn't survived' that's what is going through your head, everyone was very silent and just coming in and out, because I thought something is wrong really wrong and I didn't want to ask that question because I didn't want the answer but I was quite calm but it was just not knowing." [25 A/N def yes]

"No, well it has only been afterwards that I wanted to ask questions, but at the time I don't think. Maybe if it was not such a traumatic situation. Maybe if I was just sitting on the ward and somebody came along and said 'Would you consider going into a trial?' I might have thought more of it and asked

more, but no it was the circumstances for me. There were just so many people in that room, doctors, midwives, anaesthetists, theatre tech, just loads of people in the room and I could not think straight. I didn't feel up to asking any questions to be honest with you. I was already trying to process too much information and I listened, I took on board what they said. I don't know whether I fully understood at that point, but I cannot even remember being able to think straight to ask any questions. All I said was yes, no, yes, no, where do you want me to sign?" [28 P/N prob yes]

"I think because you are in the middle of labour and you have got high blood pressure. I think I probably could of but because my contractions were really painful and shortly after I said yes I was given diamorphine so I was sleeping and waking up and I didn't ask anything. I didn't even know what pre-eclampsia was. I would have liked to have known even when I was in labour and too out of it. They could have asked my partner or my mum because afterwards I had loads of questions and I asked my partner and he said 'I never asked' I said 'well we should of' especially with your first baby everything is so new and you don't want to ask I think you feel that your putting people out and you should just let them get on with what they're doing but when it's your second or third you want to know everything but with your first you are a bit timid and in awe of everything that's going on. I do feel that you don't ask questions because you have got high blood pressure and everyone is rushing round you just leave people to get on with the job and I know that I felt not intimated but you don't want people to get fed up with you if you ask too many questions you just want everyone to stay on good terms you don't want everyone to think 'oh god here she goes again!' So you keep quiet." [29 A/N not answered]

"Whoever it was doing it did say to me 'ask any questions you want to ask, any information we are prepared to tell you'. I just did not because I had enough going on and I thought 'oh god I'm not going to ask any questions just give me the information and I will decide." [27 A/N prob yes]

For those women who did ask questions, it was apparent that what they required was reassurance regarding the potential harm associated with

magnesium sulphate to their unborn baby and that such reassurances were readily available from staff:

> "He *[partner]* just asked if it would harm me, and then when they said no he was fine, Yeah, just would it harm me or like the kids, but they said no. I wasn't concerned because they settled all my worries down once I asked them questions anyway, the main question was it is going to harm me or me kids and they said no - so it was ok." [22 A/N def yes]

> "I think I asked if there was any risk to children, because obviously I would not put them at risk, she just said none." [34 P/N prob no]

> "There wasn't really a lot I could ask apart from the usual was there any side affects? Is it going to harm me or the baby? There wasn't." [26 P/N prob yes]

> "Well it was first mentioned when I was actually in the delivery room. I asked her 'Were there any side-effects?' and she said 'there was a slight risk if you did receive the magnesium sulphate that you would be more sickly' that was it." [37 P/N def yes]

Others did not ask any questions as they felt they had adequate information:

> "At the time we should of asked more questions, but I didn't give it a second thought. It was just yes." [40 A/N def no]

> "I probably did not, I probably thought at the time it was ok, I have got enough information." [31 A/N def yes]

> "I don't think I did because we found the leaflets we had been given had everything in" [32 A/N not sure]

Those women who did not ask any questions at the time of their randomisation to Magpie were asked to consider what they would have asked, had they thought of doing so then. Their questions paralleled very

closely to those of women who did ask questions and related largely to potential harm to their child and to themselves:

"I would probably have asked more about the long-term if there were any side-effects? the long-term side effects for me or for baby? but at the time I did not really think at all about asking about that. I just got on with it. I probably would have asked more about the, obviously the doctor should not have given me an opinion, but I probably would have asked more about what percentages it had helped and what percentages it had not helped? to help me decide whether it was the sensible thing to do or not. I would definitely have asked a few more questions about how it would affect my baby? I think I would have wanted to be certain that it did not affect baby." [09 A/N prob yes]

"I probably would have asked what would be the outcome and would it be harmful to the baby? would it be harmful to me and if it wasn't working what else would they do to try and lower the blood pressure? If they asked me to do it now I would probably say if I was given the drug would I have any side-effects from it or did they know of any? Would the baby have any side-effects? If I wasn't given the drug and my blood pressure wasn't dropping what would that do to the baby and what would it do to me and what other drugs would they try to lower the blood pressure and if the blood pressure wasn't lowering would it mean I would have to have a caesarean or emergency delivery? If they asked me to do it again I would ask that question not matter how much pain I was in, I would just know at the time to ask more questions to make sure you knew all the advantages and disadvantages before you said yes and not to feel that they wouldn't treat you the same as someone who had said yes if I said no. I think it's just because with the first baby you're more delicate I think the first time." [29 A/N not answered].

"The effects I think, you know any potential ill effects of it? Could it have done me any harm? I knew that I might get it and I might not because of the type of trial and I did get it would it have had any adverse effects on me? I think probably I would have asked that but at the time I did not care." [28 P/N prob yes]

"Would it have harmed baby? I don't know whether I would have asked that" [23 P/N prob yes].

"Just more in general, why, how long for, how many other people had been involved, how long the trial had been going on for? I don't know, you are asking me again after I have given birth. My brain works different know from when I was carrying. I then automatically thought about the baby before myself, to some degree. How many women were on the trial? How long it was going on for? Just to see if a lot of people had been on it for years they would have know more about the side-effects they would have know, not if it was dangerous because they would not have given it in the first place. Is it possible that it is going to be standard practice? or is it in the early stages of research? that sort of thing. It would not have made a great influence in me saying yes or no, but it would have been interesting to know. I was so trusting really." [17 P/N prob yes]

"I would probably have wanted to know more of what it entailed but at the time I just didn't ask because I signed it, if I had been approached earlier I may have had different views but with actually going into birth with her it was just sign this if you want and I did and that was it." [35 A/N def yes]

"I don't know I probably would have asked maybe more about what the study was about really. I knew it was a study on pre-eclampsia, probably would have asked a bit more about that." [19 P/N def yes]

7.4 Voluntariness of joining

The responses from some women clearly showed that they understood the voluntary nature of joining the Magpie Trial and that they did not feel pressurised by the clinician to take part. This was indicated by the use of phrases such as: 'she did not put me under any pressure" [31 A/N def yes], they did give me a choice [25 A/N def yes], and I could have just said 'no go away' [18 A/N def yes]. Previous studies have reported similar findings (Kenyon and Dixon Woods 2004). It appeared from the responses that the voluntary nature of the trial was valued:

"The midwife in the delivery room said it was my choice and there is no pressure. She was pretty good actually. She just explained what it was all about. She explained it was more my decision and there was no pressure and they would not come back to me and ask again, it was just one chance and if I signed it, I could do it. They were really good actually. She said we can't push you either way; it has to be your choice. Nobody can push you and nobody can make you if you do not want to do it, it's your choice." [16 A/N def yes]

"I did not feel under pressure to join. She sold it in a way that we felt perfectly happy to be involved." [08 A/N def yes]

"I did have a choice. I definitely had a choice I was not forced into it. It was completely my choice to take part. I just did not realise what I was taking part in at the time, but I definitely had a choice." [19 P/N def yes]

"If I remember rightly, she said 'have a think about it it's your choice and you don't have to do it'. She made it quite clear it was my personal choice." [13 A/N def yes]

Willingness to participate also seemed to rest on the women's awareness that they could withdraw from the trial at any time. For four women who volunteered this information it appeared this did positively influence their decision to join:

"She said 'if you wanted to come out there is no problem', she said, 'if you have got a lot on your mind or you have got other things to think about you can opt out no problem'. She was a very nice lass and she made everything perfectly clear." [07 A/N prob yes]

"They basically said if I remember correctly that an extra drip, but if at any point you feel you do not want to continue you can ask for it to be stopped. So I basically thought what have I got to lose, not in the best possible circumstances here anyway. I might as well go for it." [09 A/N prob yes]

"I knew it was a drip which you had for about 24 hours, any side- effects, or it was not suiting me for any reason I could come off. I seem to remember they said there were very little side effects and if they thought you were having any side-effects then you would be immediately taken of it, or it was not suiting me for any reason, I could come off." [17 P/N prob yes]

It is possible that, had all the women been asked this question directly, they would not have been aware of their rights of withdrawal. Other studies such as those by Jenkins and Fallowfield (2000) and Lynoe et al (1991) have identified that trial participants are rarely told they can leave the study at any time and still be treated. One woman described the moment she asked for the trial treatment to be discontinued. In her account it is evident she was aware that the trialists could still use her data. It is apparent, however, that this information was gained some time after joining the trial, and she would have appreciated knowing at the time:

"I came off the trial, I decided. I was also told by the midwife that at any point I had to say I don't want to do this. I thought 'I will not do that, what is the point?' but when you have sat there all day and there is no reason, my blood pressure had started to come down, there was no reason for me to be there, the baby was screaming, so much was going on, I felt I wanted to get back on the ward. I decided to come off that trial. Now I was not told if that would effect it, I was not told if my results could still go through or you have come off it so that goes in the bin now, that has been a waste of time. So when I got notification from you that was nice to know that it was not a waste of time. It would have been nice to know that at the time, to have told that really. It was like, 'ok lets get them tubes out of your arm, right upstairs' and that was the end of it. Now, I did not think about it at the time, but now you think I would have liked to have been told that. That is the only thing I can say, and that was from me coming off the trial. I would have liked to be told at the time that your results will go through. It made me feel at least I helped in some way."[39 A/N prob yes]

Some women identified the value of research *per se* and thought it was desirable to take part, even a person's duty. Participating improved their

personal experience, made them feel 'glad' and 'honoured'. Similar to the findings by Baker et al (2005) some women wanted to 'give something back to the hospital' to show their gratitude for helping them:

> "If people joined in more trials, I think people should volunteer for trials if they are in a position, they should do it." [36 A/N def yes]

> "I think if it wasn't for research you know, I think its good that research is done and I think if we didn't take part in research then we wouldn't have all these drugs so I do believe in research. I am glad I did take part in." To be honest with [baby] being IVF - well I thought the hospital had given us this opportunity to have [baby] - so I thought well, that's why I didn't mind helping out on this. I thought they have done a lot for us to be able to have her, so you've got to give a bit back haven't you?" [25 A/N prob yes]

> "I felt a bit honoured. I had gone through something that other people wanted to learn about and I am all for research. I mean if people can stop this happening then I am all for it." [11 P/N def yes]

> "I think – it sounds really awful – but I think if you are really kind and you think about other people then you should, then you're thinking about the welfare of other people, no I think you should help other people out." [22 A/N def yes]

7.5 Influences on decision-making

7.5.1 Reassurance from attending clinicians

Internationally there was considerable variation in the use of magnesium sulphate as a prophylaxis for pre-eclampsia prior to the Magpie Trial commencing (Magpie Trial protocol 1998). In the USA, for example 99% of obstetricians used it (Lucas et al 1995), compared with only 40% in the UK (Gülmezoglu and Duley 1998). Despite this use at the time magnesium sulphate was not proven to work as a safe preventative treatment against eclampsia. It was apparent, however, that some women (n=11) had little appreciation of this, raising the question as to whether recruiting clinicians omitted, albeit unintentionally, to explain this. After being told by the clinician

they were at high risk of having an eclamptic fit most women were reassured by the clinicians that joining the Magpie Trial would expose them to a potentially beneficial treatment. Examining the responses in relation to the women's relationships with their clinicians highlighted that the influence the clinicians had was key to the decision-making process of the women.

Previous research (Mohanna and Tunna1999, Jenkins and Fallowfield 2000) has acknowledged trust as being an important influence on participants agreeing to research; and has demonstrated an association between medical mistrust and declining randomisation (Wilets et al 2003). The study by Jenkins and Fallowfield (2000) examined participants' reasons for accepting or declining participation in randomised clinical trials for cancer therapy. They found trust in the doctor was the *most important* [my italics] reason for accepting participation in the trial. Examining more fully the reported professional-patient interaction and the contribution this seemed to have on the consent process in Magpie highlighted that the positive emotional support given by the clinicians clearly influenced the women's decisions to join. The women's accounts in the Magpie Trial demonstrated that they had considerable faith and trust in their clinicians, and this appeared to be a motivator to joining:

> "I knew they [*clinicians*] would not give it to you if there was any serious risk to me or the baby. They would not do it if there was a serious risk, they were trying to get rid of it not produce more." [30 A/N prob yes]

> "I just automatically trusted them I suppose." [15 A/N prob no]

> "I suppose I just trusted that they would not give me something that would be harmful to my child really, or to me in the long term effect. You trust that the doctor would not give you something that is going to give you a long-term problem. You have to take advice from the people who know more about it than you, so that is probably what you do at the time. You trust that the people who are telling you these things, they obviously know more about it than you do." [09 A/N prob yes]

"I am assuming that he would not ask me to do something. I suppose 99.9% of doctors would not ask you to do something that is harmful. It was the same consultant, the same two who I had been seeing throughout the pregnancy. They came and talked to me about this trial and would I, I cannot remember what they really told me. They assured me that it would not harm me; it would not be harmful to the baby." [10 A/N prob no]

"I do not think they would have given me anything that would have been detrimental to my health. Anything anyone gives you in hospital is all for the best. Whether it works out to be the best in the end is a different thing. They always do it with good intentions." [17 P/N prob yes]

These findings are similar to those of Snowdon et al (2005), in that many of the women felt that a trial would only be offered if clinicians felt it was safe and would improve their situation. This finding is also comparable to that of Kenyon et al (2006), who describe pregnant women agreeing to a trial of antibiotics in labour as relying on the credentials of the hospital, the health professionals, or the research process, and trust that neither they or their babies would be exposed to anything hazardous.

One woman who had evidently developed a good relationship with the midwife implied joining was to help the midwife in some way; also suggesting the manner of the actual approach was influential:

"I think it has a lot to do with how you are approached because of the way the lass presented it and because she was nice lass I felt like I was helping her in some way and if it was presented again in the same way I would do the same no problem. It was just a case of she was part of the study and she was co-ordinating the study and would I consider going on 'her' study or part of 'her' study because I think she was doing it for her degree or for something else as well so it was part of her education so there wasn't a problem because she was so approachable there wasn't a problem at all. I didn't do it just for her because she was a nice lass I was trying to do it, obviously, to help people in the future, or I thought I was going to help people in the future." [07 A/N prob yes]

It was not clear from the women's accounts whether individual clinicians were aware of the influence they were having over the women. However, the influence professionals can have over the vulnerable patients in their care is well documented (Oakley 1984:213, Donnison 1988:53, Lewis 1990:1, Foster 1991:79, Roberts 1992:176, Lavender et al 1999, Habiba 2000). There were examples of considerable trust in the interactions between the women and the clinicians in Magpie. Trust between patients and clinicians being the cornerstone of clinical care, care regarding a clinical trial is an extension of this relationship.

7.5.2 Therapeutic misconception

Some women saw joining the Magpie Trial as a vehicle for obtaining the 'active' treatment; and for getting a drug that they would not otherwise receive, but which had been suggested to them by the recruiting clinicians as one that would prevent them from fitting. As a result they believed the research intervention to be beneficial to them. This lack of appreciation that proposed treatments are not always beneficial and the interpretation of the research intervention as a true therapeutic option was first described by Appelbaum and colleagues (1982) as the 'therapeutic misconception'.

Appelbaum and colleagues (1982, 1987) report the findings from case studies of two psychiatric research projects: the first examining the effect of social skills training for people with chronic schizophrenia (non-randomised), and the second addressing the efficacy of two medications for the treatment of personality disorder (randomised). In examining the participants' understanding of the respective projects, the researchers concluded participants from both judged the research interventions to be assigned on an individual basis, based on the patient's particular need, sometimes by fabricating a therapeutic reason for the process. For example, they believed allocation was based on either: each person needing different treatments, the patients' 'thinking capacity', how they performed in the consent interview, their mental ability, or IQ score. Although some patients did state the trial treatment was by random allocation, they were unable to accept this was so

for themselves, and preferred to believe their trial treatment was based on their own clinical need.

The same authors in subsequent studies confirmed their earlier findings (Appelbaum et al 2004, Lidz et al 2004), as have others (Snowdon et al 1997, Featherstone and Donovan 2002, Ballard et al 2004). Lidz and colleagues (2004) consider overestimation of clinical benefit from an experimental intervention, as well as underestimation of potential risk of harm to be part of the therapeutic misconception. Therapeutic misconception was displayed in the rationale the women gave for joining the Magpie Trial; with lack of collective recall of any potential risks resulting in an overestimation of the potential benefits. Many considered their involvement in Magpie to have little or no risk to themselves or their unborn baby:

> "They explained that the magnesium sulphate would bring my blood pressure down, and even though I was told one would be a dummy, I still did not click that I could have a dummy. Even though I was told one was a dummy, I still did not think well I could have the dummy, I just thought yes I will have it" [24 A/N def yes]

> "I knew that they wouldn't have given me something that wasn't going to work for me or make me poorly so I was quite happy." [07 A/N prob yes]

> "I just thought that cannot harm the baby and the way it was explained I got the impression that they had already got an idea that magnesium sulphate was of benefit. I thought it can't hurt. I probably hoped that I would have got the magnesium sulphate. I hope I do not get the dummy if you like. I hope I do get it. [03 A/N prob yes]

> "In my own mind I thought it can't be harmful at all. I believed myself that it would be worth doing and if there was that a tiny risks that it might have an adverse effect. I felt as if and felt confident that it wouldn't have an adverse effect. [04 A/N prob no]

However, not all agree with the premise that overestimation of direct benefit from the experimental intervention is part of therapeutic misconception. Horng and Grady (2003, cited by Henderson et al 2007), argue that this phenomenon is different from and not integral to misunderstanding the nature and scientific intent of research. Henderson et al (2007) suggest there is confusion regarding a consistent definition of therapeutic misconception in the literature. They have recently proposed a new definition of therapeutic misconception. Their definition is that "therapeutic misconception exists when individuals do not understand that the defining purpose of clinical research is to produce generalisable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial". This definition does not include overestimation of the possible beneficial consequences of an experimental intervention. They do recognise that therapeutic misconception may lead to overestimation of benefit, underestimation of risk or harm. However, they argue that none of these results in a necessary consequence of therapeutic misconception; each could arise independently and coexist with an adequate understanding of the purpose of research.

Using Henderson and colleagues' (2007) new definition of therapeutic misconception, it is apparent women participating in the Magpie Trial were not encountering this phenomenon. Although contradiction in their accounts was evident, all understood they had joined a randomised trial and consequently were having their treatment allocated at random. Their accounts do though demonstrate the complexity, and subtlety, of their understandings about randomised trials.

7.5.3 Unwitting coercion

There was limited appreciation of the potential harm for both the woman and her unborn baby, and a clear belief among the women that magnesium sulphate was beneficial. Women also appreciated that irrespective of which trial treatment they were randomised to they would not be denied magnesium sulphate if this was clinically indicated, i.e. when having an eclamptic convulsion. This made some women unconcerned regarding the implications

of joining. Because of this, the Magpie Trial presents similar findings to those of Canvin and Jacoby (2006): joining being viewed by some with 'apparent indifference', as a situation where there was 'nothing to lose'. Similar to the situation described by Canvin and Jacoby (2006) the Magpie Trial clinicians may have been excessively confident in their description of the trial. The theory of clinicians being overly optimistic and over simplistic in their description of trial treatment and trial design, as reported by Canvin and Jacoby, has been described previously as representing a form of 'unwitting coercion' (Little 2002).

> "I said no I have not been told about the Magpie Trial, what exactly is it? He was saying that he had worked in Africa, in every other country bar this one they give magnesium sulphate to pre-eclamptic women and for some reason this country will not believe that it does help to stop pre-eclampsia so if you would not mind would you take part in the trial or words to that effect. I cannot remember everything, but words to that effect." [11 P/N def yes]

> "I asked if I did get worse what would happen and she said we will take you off this and we would give you magnesium sulphate because it has been tested and that will help if you do get to eclampsia. I thought fair enough, that was what decided it for me thinking back." [11 P/N def yes]

> "She said in America they gave magnesium sulphate routinely and yet it wasn't proven in this country and it would prevent if not a first fit then it would certainly prevent subsequent fits and that's how it was explained to me. I felt reassured I suppose because it was being used anyway and it wasn't something that was completely new and potentially life threatening they did not know about so it was reassuring really that there were probably no risks involved if it had been passed in America. My understanding was that it was fine to join the trial because America was already using the drug. I didn't feel that it was any danger the drug because it was obviously being used routinely anyway and in my experience to get anything past the FDA they can be far stricter then we are over here so I didn't feel a total guinea pig for a drug that was completely new on the market and you were completely going into the unknown there was a security there that it had been used before in a developed country so there was that security side to it. That was

obviously reassuring going into it and whether if you hadn't have had that I wouldn't have done it I don't know really. But that was definitely a pull I was confident that there was going to be no surprises if you like." [37 P/N def yes]

"I felt like the research had been carried out for a number of years and it wasn't a new trial, it was newer here than abroad. I think I was told it had been tried through Europe more than here. It wasn't a new trial, it was like one of the first people, and it was more that it had been going for 2-3 years. It must be ok." [16 A/N def yes]

7.6 Quality of information received

Previous studies have explored women's views and experiences of maternity care and have identified that women have markedly different preferences regarding information provision in pregnancy; either in the amount and detail they require (Emslie et al 1999, Levy 1999, Jackson et al 2000, Rowe et al 2002, McLeod et al 2004), the format in which the information is presented (Kirkham 1989:129, Cooper 2001, O'Cathain et al 2002, White et al 2003) or the time during their pregnancy when they require it (Segiun et al 1989, Mohanna and Tunna 1999, Raynes-Greenow et al 2007). Evidence from QUOTE supports this literature, in that women recruited to the Magpie Trial had noticeably differing requirements regarding the amount and content of trial information they sought. However, generally they felt that they did not receive an adequate explanation or level of detail about the trial prior to joining.

Women discussed several issues regarding information provision and gave suggestions of what they would have liked to receive. These included: what the aim of the trial was, what it was hoping to find out in relation to pre-eclampsia, how the trial treatment might work, the possible risks of joining, and how the trial would be administered:

"I didn't know what it was for, whether it was to bring my blood pressure down. No one even mentioned fitting that was completely new to me. It is the details of actually what it is for more than what it does." [40 A/N def no]

"In hospital they really did not go through it with you, and I think they should have done, gone through it a little bit more to explain what would happen and a bit more information about the trial, no one mentioned it then, for instance - how many people were taking part and when the results would be coming out and what things would it improve for pre-eclampsia, because no one really said it would stop convulsions or it would stop you from developing high blood pressure, they just did not explain it very well. Someone should have given more information or at least come and explained it." [30 A/N prob yes]

"They didn't even mention that I would have a drip in for 24 hours. The next thing was I was told I had to wait a couple more hours to have the drip taken off, as it had to stay on for 24 hours by a different midwife. I said I wasn't told this yesterday, well obviously the midwife mustn't of said anything to you about it. That was it really." [15 A/N prob no]

"I was never told, it was only when we have had a chat before *[follow up study home visit]* and we have gone into detail that I knew the risks. I was not told the risks and I think it was just a rush to get me down. She wanted to get her trial started I suppose you have so many. No I do not think I was given enough information, I really don't." [39 A/N prob yes]

Regardless of the above findings, it is vital to highlight that many of the women felt that their experience of receiving information about the Magpie Trial had been positive, and several made comments of an encouraging nature about the trial and they way in which it had been explained to them by the clinicians:

"She just explained what it was all about. It was a national trial and it was a good thing. She explained it was more my decision and there was no pressure and they would not come back to me and ask again, it was just one chance and if I signed it, I could do it. They told me what the procedure was to go ahead, I would have to have a drip in and I would have to be probably catheterised afterwards and rest for 24 hours, but it was fine! They were really good actually. I was thinking about the baby. They had explained what it was and I understood what she meant." [16 A/N def yes]

"It was explained really well, the lady who explained it she was very relaxed and was not in a rush. She said I could ask questions. I could not see any other way for her to do it at that particular time that would have been better. As I understand that they wanted to start it straight away, then I cannot see any other way than asking me after having the baby which would not have been much good." [27 A/N prob yes]

"They really explained. They sat and explained to me with it being a trial they don't know exactly who is getting the drug and who isn't. It was all explained to me really well." [36 A/N def yes]

"The way I was approached was quite nice, you got this 'we are doing this, would you be interested in this?' Gave me some information to look at and came back later. Nine times out of ten you have-not looked at it when they come back, but it was very relaxed, you don't have to if you don't want to, which I think is good." [06 A/N def yes]

"As I say it was very well presented the lass had obviously done a lot of work herself on it and I think when people are more informed on things and they put in a good case for and against and provided they know their subject I think most people will help. The midwife that presented it she was very clear and concise and she told me the ins and outs and the fore and against. You can't force people into doing it but as long as you've got a good ambassador for it people will volunteer and as I say she was a good lass and there wasn't any problem." [07 A/N prob yes]

Conversely, being overloaded with information and giving explicit descriptions of their situation was also seen as problematic for some women. This parallels the work of Corbett and colleagues (1996) who, in their study of opinions of the public, found less explicit statements relating to research were more favoured than those openly describing the process. Women involved in the Magpie Trial appeared to prefer not being given a full and frank description of the trial or their condition, perceiving this additional information as either unnecessary or creating anxiety:

"It is only afterwards when you read what pre-eclampsia and plus the HELLP Syndrome that I had is that you think 'oh my god!' It's like if I had know all that I would have been, I think my blood pressure would have been even higher. No, I think probably for me I had enough information that I needed. I think at the time the information I was given was as much as I could have taken in with everything else that is going on at the time. It is not like you are progressing in labour normally and have this to read while you are just going along. It is thinking about things, you have got drips in your hands and everything like that and blood pressure monitors going off every ten minutes and things like that and catheters. I think it was enough, I think otherwise you could just get too much information. I do not think we need to be over informed of the in's and out's of why people are taking part and where it is, you know?" [05 A/N def yes]

"I think if someone would have said when I was two months pregnant this trial is going on I think it would have scared me. You know 'oh my god those terrible things could go wrong with me!" [08 A/N def yes]

"To be honest with you I was already trying to process too much information and I listened, I took on board what they said. I don't know whether I fully understood at that point, but I cannot even remember being able to think straight to ask any questions. [28 P/N prob yes]

7.6.1 Degree of simplicity of information:

For women who had difficulty comprehending the trial information, the language the clinicians used to give their explanation about the Magpie Trial appeared to be the cause of misunderstandings. Women stated that clinicians provided oral information that was too technical for their grasp; and that the concepts used by the clinicians to describe the trial were often unfamiliar to them. Women wanted the information to be in a clear, simple, lay language and presentation:

"I suppose if she had explained exactly what it entailed as in 'we are just going to attach this line and somebody is coming to check you reflexes such and such a time', I suppose if she had simplified it. I think because it was all about the magnesium sulphate, once that was said it was like a term like the

'surfactant', you think 'oh no it's another medical word'. Husband, he was blinded by science. I think if it had been simplified somewhat, If it had been explained to me that it is just a simple thing I would not have minded. I think if they can explain these trials in as simple a way as possible, so that you are not frightened by it. The chap who was telling us gave us his sales pitch in the words he had obviously come to use and when he hit a blank wall he did not know how to explain it in a more plain English way. What I had to do to make my decision was I had to ask him: 'the way you have explained this trial to me, I think it is x, y z am I right?' and I actually had to ask him 'is this what you are telling me?' I actually had to come up with my own way of interpreting what he said." [03 A/N prob yes]

"It was told to me in words I would not normally know or use such as placebo and things like this, other than that I could not tell you the exact words, only what I remember understanding about it really." [27 A/N prob yes]

"The midwife asked me if I would consider it and gave me the leaflets and then came back with the doctor and both of them explained it to me. Not that I could really understand the doctor. It was the midwife really who explained it to me she explained it sort of in our words, you know, because doctors give you all these big words don't they that you don't understand? Everything that they did, step by step, she explained it. When the doctor explained it to me he could have used those words, but I looked at him as if to say 'I don't understand' and the midwife sort of translated what the doctor meant." [36 A/N def yes]

Researchers have often overlooked evaluating the provision of oral information in simple lay language in favour of evaluating the provision of written information patients receive, both within and outside research situations (Priestly et al 1992, Dixon-Woods 2001, Ferguson 2000, Akkad et al 2004, Kenyon and Dixon-Woods 2004). The acute setting the women were in at the time undoubtedly magnified problems associated with information provision, and some women stated they would have benefited from having the trial information repeated:

"If you are not familiar with research and pregnancy. I think if it is mentioned when you first come in and if they do have a chance to come and talk to you a second time, it would be helpful. Even if they had spoken to you it would be acceptable to come back and have a recap again. When it was first mentioned to you and you had only just come in and everything was up in the air and to have another chat about it later, to let you know if you are happy about it. I think the earlier you can approach people, the better. Like I say if you do have time to go back and talk about it again, I think it would be really valuable. " [04 A/N def no]

"It would have been nice to have had a follow-up or things explained more fully when you were in more of a stable mind and not in any pain and then you could ask everything you want to ask and get everything explained to you possible." [29 A/N not answered]

Need for repetition and elaboration of information is highly individual. The practice of continual informed consent as a longitudinal process rather than the mandatory event occurring prior to enrolment in clinical research has been recommended as a way of reinforcing participants' understanding over time as they gain experience being study participants (Faden and Beauchamp 1986:151, Schaeffer et al 1996,). A recent study (Allmark and Mason 2006) raised the question whether continuous consent, a process in which information is given to research participants at different stages in the trial, would ameliorate the difficulty brought about by obtaining consent in emergency situations. The TOBY Trial (Total Body Hypothermia Trial) required parents to provide consent at a time when their newborn baby had a life-threatening illness. Researchers in the TOBY-QUAL Study gave some of these parents additional information at later points in the trial and evaluated whether they assimilated this 'staged' trial information better. The researchers conclude that using this continuous process did help clinicians obtain more valid informed consent.

7.6.2 Staff not always knowledgeable

Contrary to the assumption that clinicians would be familiar with the design and purpose of any trial they collaborated in and recruited to, a number of

women in the QUOTE Study described instances where the recruiting clinicians appeared not to be familiar with some aspect of the Magpie Trial. This finding concurs with those of Mohanna and Tunna (1999) and a more recent study by Ziebland and colleagues (2007). Zeibland interviewed surgeons recruiting to the Spine Stabilisation Trial and concluded that many were not familiar with its purpose or rationale of the trial. Although the QUOTE Study did not examine understanding of the Magpie Trial from the perspective of the clinicians and did not directly ask those women recruited for their opinion of the clinicians' knowledge of the trial, it did appear from their comments that there were some similarities with Ziebland's (2007) findings. Women perceived that some clinicians lacked the necessary knowledge to provide an adequate explanation of the trial:

> "I knew there was a minimum risk of things going wrong, but I don't think they *[clinicians]* knew that much about it themselves. If they'd of been trained more on it, maybe that would have helped them, as it was a new thing. I mean about the trial now. I know pre-eclampsia has been out for a while, but it is just if they had been trained on it more. They could of helped mothers more, or if it was someone like yourself or a midwife who has been through the experience and someone there who dealt with just that side of it. They were just a bit, I don't know, they just didn't give me that much information back. Then I'm not so sure if that was they didn't want to worry me or concern me. You have to weigh up the pros and cons really. Because what benefits me may not benefit someone else from different background, different culture. I didn't know enough at the time, but I am glad I knew what I did. But knowing a bit more I would of felt better in myself, maybe if I had someone there like who could advise me, in that type of capacity?" [16 A/N def yes]

> "There was two of us in the ward having twins. Me and the other girl, we came quite friendly because we were in for such a long time. She was having problems as well with her blood pressure. The midwife used to come around every day asking if we were interested and then on one particular day she came to us two and sat us down together. She was nice, but she did not seem to know a great deal about it and there was not much information and we felt pressured by her. Well I did personally." [34 P/N prob no]

"I don't remember the information being that clear. I don't remember her being very clear about what would actually happen or when it would be administered. I'm sure she was quite vague, but she did give me leaflet to be fair." [04 A/N prob no]

7.7 Involvement of others in decision-making

As previously described, women eligible to join the Magpie Trial were in an emergency situation, some critical. As with most hospital emergency situations, partners, family members or friends are able to be with the patient throughout the critical period. Maternity care is no different from other such specialities, and clinical staff actively encourage family members to stay and provide emotional support in these circumstances. Research in the neonatal period (and so not fully comparable) has identified that women considering joining a trial on behalf of their baby found it more problematic without their partners' support (Snowdon et al 2005). The women in the QUOTE Study were therefore asked who was with them at the time they were approached about the Magpie Trial and what influence, if any, on their decision to join this person(s) had.

7.7.1 Role of family members

Most women (32), as would be expected, had a support person with them when they were asked to consider joining the Magpie Trial: for most it was their partner, for others an additional family member. It was clear from the interviews however, that although these people could be present they did not, in the majority of cases, play a significant role in the decision-making process. It was apparent that it was the women themselves who ultimately made the decision to join. The reasons given for this were that it was the woman herself who would be receiving the trial treatment and it was therefore her right, ultimately, to choose:

"My husband was there. But I just did what I felt was the best thing to do. I would think that most women make the decision on their own, the way that my husband looked at it is it is not being administered to him it's my body so it's my decision." [12 A/N def yes]

"He basically said it was up to me because I was at the end of the day having the drip. So it was up to me and it was my decision." [15 A/N prob no]

"It was my decision. I think my partner knew at the end of the day it was my decision. I talked particularly to my sister-in-law because she had a baby of nine months. The only thing she said was 'I couldn't do that because I couldn't have that needle in my arm' and all that business and other than that, that was really the topic of conversation. Yes it was just very much my decision." [13 A/N def yes]

"I think my partner was with me. He had been with me most of the night. Yes I think he was there, I don't know whether he was asleep, but he was there. I do not think we discussed that. We left everything that would happen to me, to me really. He was in awe of baby at the time. I think they spoke to him and said do you think she understands what we are saying. I said 'yes' because I overhead them asking. So, I don't think we had a great deal of discussion, no." [17 P/N prob yes]

For most then, the women's decision to join the trial was their sole responsibility though with the support of a partner. This was irrespective of whether the woman had already delivered. Some women however, did acknowledged that their partner or support person played a relatively small part in their decision to join Magpie:

"I honestly believe he had input, because he does have an input, but it was my decision to take. He said that at the time. He said it sounds a good idea, I already had the idea going through my head, I knew it was a good idea, the input he gave, it was already going through my head. It was my decision." [39 A/N prob yes]

"I was not bothered, but I just wanted a second opinion from my friend. I just said what do you think? I remember her having a look at the leaflet. I did not mind, just thought if she had said there was a chance of something happening or no maybe you should not, I would have changed my mind, I would have said no, but I was happy to do it. I have not got any problems with doing it." [31 A/N def yes]

"I think it was a kind of, you know my husband tends to let me make decisions about things I am doing obviously, but I wanted his opinion and in that respect I think it was a joint decision that we thought it was the best thing to do. I think it is good, well obviously he is the father of the baby and he is my husband so I think as a patient it is nice to have somebody else who is not part of the medical profession to be able to sound off to see whether you are making a good or bad decision and then you know if you are both in agreement." [09 A/N Prob yes]

"My husband was there as well when they were talking about it so he was able to concentrate rather more on what they were saying than I did. I did say to him do you think we should do it and he said it is up to you, but it sounds ok. He kept an eye on what they were doing so I was quite happy to do it. He gave me more confidence because he was there to make sure that I understood what was being said to me because I was in labour. I did say it back to him is it and he said that is what I understood anyway, so that gave me more confidence that I understood what was happening. Perhaps if he had not been there I would have felt far more insecure about going on the trial because I would not have been as confident that I understood what was going on. I felt I was ok agreeing to it but I did have to bounce it of my husband first. Because, I think you do any way, at that time your mind is not fully on what people are asking or telling you." [10 A/N prob yes]

Sometimes, their partners played a more active role and were more influential:

"It was a joint decision. Well he was there when we were talking to the girl *[midwife]* who came, so all three of us chatted about it. When we had established it was safe and what part we would be playing in the trial, we were happy that we could fulfill our side of the deal without it affecting three of us. If he had given some good reasons for his objections that I thought was valid, I would have agreed with him, but if they had said 'there was a slight risk' and I said I wanted to go ahead, and he said 'look at the risks' I might have declined then, but no I think we both agreed there was no reason not to take part. To be honest if he had said no I would probably not have

bothered with the trial because of how it was, you know you are in hospital, I was dreading the birth, that was my main fear, you know pain, injections, so I would have agreed with him and not bothered." [08 A/N Def yes]

"The midwife like explained the Magpie Trial and what you were trying to do - and I agreed to it - well I asked my partner first and then I agreed to it." [25 A/N Def yes]

For the eight women who were approached to join the trial while on their own, it was apparent from the responses their partners had only recently left their side. For all but one of these women being asked to join the trial whilst alone did not seem problematic in contrast to other research (Snowdon et al 1997):

"I just did it on my own. They asked me did I want to discuss it with my partner before I started the trial but to me it was my choice, it was me that was carrying the baby, it was me that was going through it and my partner would have said 'if it makes you better do it anyway' so I just did it. I just said yes without asking, really." [36 A/N def yes]

"It was just me, it was during the night anyway because it was the nurse that was on nights so I was there on my own basically, she was finishing work after the night-shift so I wouldn't have seen her again. It was just me and I thought it was my decision anyway and all I was concerned about, as I said to you before, was that I wasn't going to be poorly either way. So it was just my decision." [07 A/N prob yes]

"I was on my own, personally it didn't bother me. It might bother some people but personally it didn't bother me. Later on he fully agreed. He said whatever you decide is fine." [26 A/N prob yes]

One woman gave a detailed description of the circumstances involved in joining the Magpie Trial. She described the effect her husband and family had on the situation and her decision to initially decline joining, only agreeing once her family had left the hospital and returned home:

"We said no straight away because we thought 'oh no another trial'. My husband did not have a great understanding of it. I think he just thought get it out of the way. Say 'no' and it will go away. I think that was his attitude to everything that was happening. Just make it go away, it's like a bad dream. It still comes back now three years later. It is not these happy births you read about in all the pregnancy magazines. The second time she came to me was better because I was calmer, I did not have anything else to think about. I had had a good look around I suppose and I was calmer because I had made the decision to send them all home. I just thought if it is my last night with the baby I just wanted it to be me and the baby and not have any other distractions and I thought if I agree as well, and I would not have the guilt of not doing it, because I did feel guilty. So, I suppose I felt pressurised in a way in the beginning, then when I turned them down and they explained it I came to the decision myself without feeling pressurised into it. I actually thought they might actually help my baby as well. Cos I thought as well if I died giving birth or whatever, he would not have a mother, so if they can stop me getting poorly it might help." [03 A/N prob yes]

7.7.2 Role of staff

As already noted in previous sections, women generally expressed an over-riding sense of trust in the clinicians, and often gave descriptions of the practical and emotional support the clinicians, especially the midwives, gave them. Their accounts confirmed how much they appreciated this support and how it contributed positively to what was a difficult and stressful birth experience:

"There is always one particular person you latch on to and there was one midwife and I must admit I did latch on to her and she was there with me holding my hand. They were trying to put a line into my neck and they could not get one in. All my veins had shut down so they were trying to put a line into my neck, and she was lovely and she was so calm and she had a calming effect and every time I started feeling uneasy I talked to her. She was my saving grace. At that point I did not mind what anyone else was doing." [28 A/N prob yes]

"The staff were lovely. As I said, the staff were so nice that I trusted them to let them do what they wanted to do basically. They were so nice I had no problems in taking part in the study. They made me feel at ease and I felt I would not come to any harm. They were lovely." [31 A/N def yes]

"They were doing their best for me, you know. I mean like when the doctor said he would stay and do the operation. I don't know whether it is just doctors but there is not, not everybody would put themselves out. You know people when they are due to clock off if you like, there is not many people today, if you get that kind of care it is a good thing to have. The nurses, I remember it is not a job to them it seems to be much more. I remember one saying to me that she was not particularly religious but that she would pray for *[baby]* and that meant a lot to me. They were doing their best, they are very well qualified people who deal with this condition, that's why I knew I was in the right place" [03 A/N prob yes]

However, some women reported feelings that they were pressurised by the clinicians to join, or that is was just difficult to say no for whatever reason:

"When I said to them it was making me feel sick, I felt as though they were pushing me on to carrying on with it. I was panicky and he *[obstetrician]* was saying just lower it *[infusion]* down and see how you go. It was like – 'you are doing it now'. I think if they would of asked me – 'would you like to stop it', yes I would of done. It wouldn't have been difficult to say stop the trial, but I would of felt as though I was putting people out. That was down to me, not having the confidence to say that I wanted to stop it."[40 A/N def no]

"I remember one of the midwives saying "if you don't have this baby now with your blood pressure as it is and your protein level as it is, in ten years time you will be in the other side of the hospital having a kidney transplant", that was what it boiled down to. They had left the baby as long as they could without damaging me but it had got to the stage where it was dangerous." [19 P/N def yes]

"The midwife used to come around every day asking if we were interested and then on one particular day she came to us two and sat us down

together. She was nice, but she did not seem to know a great deal about it and there was not much information and we felt pressured by her. Well I did personally. She did ask us if we wanted to make a decision then and none of us did, but then she came back every morning, asking have you made a decision yet. I feel like I was pressured because she was there every day until we agreed to it." [34 P/N prob no]

"I had already been in hospital for a month and I was feeling quite institutionalised and didn't feel like I could say 'no' to anything. I was saying to my husband that 'if I go into hospital this time *[pregnant again at time of interview]* I am going to be a real strop'. It was my first baby and I just thought everybody must know better than me." [04 A/N prob no]

"I think because you are in the middle of labour and you have got high blood pressure I think you feel that *[you]* may not be given the same treatment if you said 'no'." [29 A/N not answered]

7.8 Conclusion

On average the women took a relatively short amount of time to consider their decision. This appeared to be linked to a number of issues, some practical, as in this clinical situation a short time to decide is all that is possible; others linked to their understanding of the Magpie Trial. Practical aspects were related to the fact that clinicians were not able to identify women and therefore approach them prior to onset of the disease, and women were therefore required to make their decision at the point of randomisation in a relatively short space of time. Others agreed to the trial with a very 'common sense approach', implying clinicians were there to look after them and wouldn't expose them to any unnecessary risk. Few said they found their decision difficult, and of those that did this was related to the circumstances at the time, rather than linked to any difficulty related to the trial *per se*. Nonetheless, when asked what their reasons were for joining the Magpie Trial, partial misunderstandings were apparent.

Chapter 8

Women's reflections on joining the Magpie Trial

8.1 Introduction

This final results chapter presents themes related to the women's experiences after joining the Magpie Trial through to the time of the follow up study. Women were asked about receiving the trial results and about being contacted a number of years later to participate in a follow up study. Members of the Magpie Trial management group felt it vital to provide the results directly to the women involved on completion of the trial. The ethos of the trial was to acknowledge the central role the women had in the trial, to promote their involvement and encourage partnership and collaboration between the women, the clinicians and the trialists. Although the concept of providing results to trial participants is not new, as far as the management group were aware no other clinical trial recruiting similar types of women (pregnant or less than 24 hours delivered) in similar situations (having a life threatening illness) had provided them with the study results directly.

8.2 Receiving the results of the Magpie Trial

There is growing support for the practice of offering research results to research participants. Recent government initiatives (DH 2005) and several prominent groups (AIMS/NCT/MA 1997) in the UK have issued policy statements addressing the provision of research results. The Department of Health's Research Governance Framework recommends that research results at study completion be disseminated promptly and fed back as appropriate to participants (DH 2005). Over ten years ago the Association of Improvements in Maternity Services, The National Childbirth Trust and Maternity Alliance, in their charter for ethical research in maternity care, recommended that women should see the results of research they have participated in (AIMS/NCT/MA 1997). The practice of offering results to research participants has received growing attention and is now considered essential practice in the ethical conduct of research, one example of this being that researchers conducting research with human participants are

required, when applying for ethical approval (in the UK), to document whether they will provide study results to participants following study completion, as well as how they will deal with the situation should new information about adverse effects that may affect a participant's willingness to remain in the study become available part way through the study (NRES 2008). Consequently these recommendations may in themselves promote researchers to provide participants with study results. The offer to provide research results at study completion acts as an acknowledgement of the valuable contribution to research that has been made by a participant.

Existing written policies governing return of research results to participants are generally supportive of the concept and universally promote the recommendation for offering results to all research participants. An automatic assumption is that providing participants with results, an intervention in itself, is beneficial. However, the practice of providing research participants a summary of the results is still uncommon and to date there is no clear guidance as to when and how this process should occur. Adherence to the guidance and decisions about the format of provision is left to the individual researchers. Furthermore, there is little recognition of the possibility that sharing research results may in fact harm participants, causing anxiety and unnecessary concern (Dixon-Woods et al 2006). It has been shown, however, that research participants have a desire for research results, and may cases wish to have the results even though they may be distressing (Snowdon et al 1998a)

On completion of the Magpie Trial all women who were recruited in the UK were posted a summary of the overall trial results (Appendix 6). The Magpie Trial management group prepared this summary in consultation with representatives of the UK-based user group, Action on Pre-Eclampsia (APEC). The three page summary began with thanking the women and acknowledging the contribution they had made to the trial; it included an introductory paragraph about the Magpie Trial (aimed as a reminder), a description of the main findings with regard to both women's and children's outcomes. The summary informed the women that magnesium sulphate

reduces the risk of eclampsia, and that it is likely that it also reduces the risk of maternal death. Also that magnesium sulphate (as prescribed in the trial) is safe for both mothers and babies, although unpleasant maternal side effects, particularly flushing, were common. Copies of the newspaper clippings of the press release the trial received at the time of the launch were also included, as were citations of the medical publications; and details of how to contact the trialists for further information.

It became apparent during the QUOTE Study interviews that six of the women could not recall receiving the results. The women were still asked, however, about their thoughts regarding provision of research results generally. Each were provided with a copy of the results after interview.

Receiving the results some years after involvement in a trial and therefore being reminded (as was the case here) of a very stressful and difficult time in a person's life could have brought anguish (Dixon-Woods et al 2006). However, providing the women with the Magpie Trial results did not appear to cause any emotional distress; on the contrary, receiving the results was welcomed by the women and viewed as important and valuable:

> "I remember reading them and thinking this is quite interesting, and reading that they did believe that it has helped and I actually thought that is really good, there is a positive outcome from that that is really good. I was quite interested when you said it was a worldwide trial." [09 A/N prob yes]

> I think it is a bad thing if you do these trials and then you never get to find out if it has helped or not because obviously there is the time element gone into it at the start. All the energy getting you to do it. I think it is a good thing you can follow it up afterwards. Otherwise you never get to know do you? So, I think it is a good thing. I did wonder and then I got a letter through that the results were coming through. I have kept them all." [03 A/N def yes]

> "It was just a case of I have done this, do I hear anything about it? I was quite surprised, I didn't know whether I would, but I did I got various correspondence as the trial progressed. It was quite nice it made it a bit

more personal. It is nice to know what is happening afterwards. I got the result and the article and that so that was nice. So it was nice having that information after I had left." [06 A/N def yes]

Women described the pleasure in knowing that future women will benefit from their participation:

"I think you felt that you had done something useful and it was nice to know that it may help someone else and it was sort of all confirmed really, when the trial ended and you got the information I think that was a very good idea and that for me I felt I had been part of the success really, something that would benefit other people and I thought that was excellent the way it was conducted." [37 P/N Def yes]

For some women it was clear receiving the results gave them some welcome closure of the trial:

"With the information coming through that it has been nice a) to receive the information and b) reassuring and nice to know that by taking part you could perhaps help somebody else. I think both of us *[partner]* have said that it's nice to know that somebody may benefit. I certainly found when the trial finished and the newspaper cuttings and the Lancet cutting you had an end to it." [37 P/N def yes]

"When you got back in touch I was made up. I said to my Mum, it is nice to see how it actually got on and that you have got back in touch to let me know the results of it. I have always wondered what the results were, so when you got in touch that was why I did want to meet you and I did want to carry on with it. To find out as much as I could, because I never at the time." [40 A/N def no]

"It was actually nice. You are sort of left dangling. Much as I did not think about it because you have a new baby, it was nice to know it was not that you had taken part in a trial that you would not hear about. It was nice that there had been that contact. It was nice to get some closure on it, because you are getting to know a bit more about it." [39 A/N prob yes]

The results emphasised how dangerous pre-eclampsia can be. This prompted the women to recall the time they were recruited and consequently the reactions of the clinicians at the time:

> "I think what did surprise me was the fatalities, the number of fatalities, that was surprising. You appreciate it's serious, you sort of gather that by the way all the clinical staff are running around like headless chickens when it happens. Something serious happens why is everyone here? The alarms go off, but when you actually see it in black and white that you know so many people die, you think crikey! I wouldn't have said it would make me anxious. I was quite proud to have taken part in something, and certainly that such a positive result had come out of it. No it certainly did not make me anxious. I think the results are a lot better than anybody could have expected. I think that's why the trial was cut short wasn't it? [01 A/N def yes]

Some stated they shared the information with a family member:

> "It was great, very interesting. I left it out for my husband and he read it. You probably get people thinking what is this? and throwing it in the bin, but I found it very interesting." [14 A/N def yes]

At the time of receiving the results, three women were aware of their treatment allocation, two of whom had been allocated magnesium sulphate (13 A/N definitely yes; 31 A/N definitely yes), one to the placebo (17 P/N probably yes). Each had requested unblinding as a consequence of the home visit. In the light of knowing their allocation it did not appear to impact on their reaction to the Magpie results. The woman randomised to placebo was no less satisfied:

> "As long as I hadn't had a fit, if things had gone exactly the same as they have now I wouldn't have a preference on it. But obviously, if things had of got worse if I had a fit or things hadn't gone the other way than they had, then maybe I would have been thinking in retrospect if I had of had it would it have been any different? I suppose you will never know either way honestly!" [17 P/N prob yes]

For the two women receiving magnesium sulphate it was evident their views were affected by their experience and not having eclampsia:

> "It does not make me feel any different really. If you thought that every patient was going to get it, just the magnesium sulphate, then it is not a trial then. I think it probably still works for some people and not others anyway. I don't think it makes any difference. I think all trials have to have a placebo in it as well." [13 A/N def yes]

> "I'm glad actually. I understood that I did have it *[magnesium sulphate]* now, but I had an idea that I did. I think it made my pregnancy easier. I don't know, as it was my first pregnancy so I have nothing to compare it to. But it made me glad knowing that maybe I got this and it was a good chance." [16 A/N def yes]

Perhaps the overall positive feedback from the women was related in part to the straightforwardness of the results. There was no harm caused by the trial drug, only benefit. Also the results did not make any difference to the women's current or future care, as their pregnancy had ended. It is possible that individual reactions to receiving the results were heavily influenced by their and their child's current health. It is also important to acknowledge that all the women interviewed were in good health as were their children, with the exception of two children; one had severe cerebral palsy (woman's code: 10 A/N prob no), the other had Downs Syndrome (woman's code: 28 P/N prob yes). The fact that treatment was randomised, was apparently not an issue for the women at this late stage.

8.3 Experiences of the follow up study

For some time now follow up of participants in perinatal trials has been considered necessary (Belizán et al 1997, Johanson et al 1999, Johnson 1997, Fooks et al 1998, Grant et al 2001). A recent Cochrane review (Halliday and Ehrenkranz 2003) highlighted the importance of carrying out long term follow up. The review of trial of babies at risk of chronic lung disease or with established chronic lung disease, who were treated with early high-dose dexamethasone after birth confirmed the need for concern when

interpreting data on short-term outcomes alone. Because the trials presented obvious short-term benefits, including reductions in ventilator and oxygen dependence in chronic lung disease, steroids were increasingly adopted world-wide, over a period of more than fifteen years. When studies with long-term follow up were eventually reported, they showed no significant increase in the overall number of long term survivors, but some reported a clear increase in the number of survivors with cerebral palsy (American Academy of Pediatrics Committee on Fetus and the Newborn 2002).

Based on such findings, the importance of carrying out long-term follow up of trial participants appears indisputable. User groups such as AIMS (Association for Improvements in Maternity Services) have advocated for some time that with all childbirth research the names of mothers and their babies should be kept so that long-term follow up is possible (Robinson 1994).

Little attention, however, has been given to exploring how participants might feel about being contacted some years later by trialists, and subsequently followed up. Mohanna and Tunna (1999) in their study exploring the views of pregnant women who had previously been invited to participate in a clinical trial found that women appreciated the contact. A narrative account of the experience of those carrying out the Magpie Trial follow up study has been published (Farrell and Duley 2007). Included is an insight into the women's experiences of follow up in the UK (Smyth and Armstrong 2007). Women, although surprised by the personal contact by the Magpie researchers were extremely welcoming. The QUOTE Study gave further opportunity to explore in-depth how the women felt about being contacted for the follow up some years later.

Although long-term follow up after randomisation to a trial does have the potential to cause upset and stress, the women interviewed overwhelmingly welcomed being involved in the follow up study. Even though they were often surprised by being contacted, as many had given little thought to the trial

since coming home from hospital, nevertheless they were still receptive to the follow up:

> "At the time I did not realise that there was follow-up and that was quite nice to know that someone was interested to come and see you a couple of years later. It was quite a surprise really that someone came to see you. " [09 A/N prob yes]

> "Everything has to be documented, it is not just the hospital it is the effects afterwards. I had it after [*recruited postnatally*], but if it was before then you would need to know if there was any effect on the children, so it should be followed up." [18 P/N def yes]

> "It is brilliant, really good. It is good for baby's progress, it has just been nice, coming out doing that study on him as a pre-term baby, and then making sure that I have been ok, taking my blood pressure. It was nice, it was like they wanted to keep in contact. It makes you feel important, coming to do the study on baby that has been fascinating, really interesting. When I got the letter saying about the follow-up trial which I thought was good. So when [*researcher*] came out and did that big hour study on him. It was brilliant, because it put my mind at rest. He was doing things I did not know he could do." [19 P/N def yes]

Women commented on the postal questionnaires they received, their comments relating mostly to the child developmental questionnaire (ASQ) and how much they enjoyed completing it, and found it useful and reassuring:

> "So, I enjoyed doing that. It made me interested, not anxious. It is interesting what [*children*] can grasp or what they can't. They can put their shoe under the table or put their shoe on the chair. It is funny how they interpret what you say. It is obvious from the questionnaire that you have to ask it in a certain way, like [*husband*] wanted to prompt him, and it is obvious you are kind of helping them. I found it interesting." [03 A/N prob yes]

> "They were quite simple to do. There was stuff to do with all of us not just me there was my husband and obviously, the baby so it was something that we

could all sit down and do so it was quite enjoyable actually, so it wasn't a problem at all. I think it has been very well co-ordinated. To be perfectly honest when they said that someone would be in contact with me I didn't think that for one minute that anyone would be in contact with me. I thought it would just be we would see you in 3-weeks and then you never hear from anyone again so when I got the questionnaire, I thought oh, right and the whole family filled it in. Then with a lady *[psychologist]* coming from Newcastle and yourself coming I appreciate its obviously a very well co-ordinated study so I didn't mind doing it." [07 A/N prob yes]

"I filled it all in and the questions you asked about baby really made me think. You don't know some of the answers and you are trying not to embellish, 'Oh of course she can do this', I was saying 'do you think she can pull the pram backwards?' or whatever. It was interesting to fill in. Yes, it made you think. Is she supposed to do this? Is she backward if she cannot do this? But no anxiety, no." [14 A/N def yes]

"I filled in the questionnaire. I was going through an awful time at the time. I still managed to fill in the health questionnaire and my health visitor had not done much of an assessment on them. It was nice to know from those questions for myself what they could and could not do. It was much more in depth than anything I had seen the health visitor do." [31 A/N def yes]

The format of the child developmental questionnaire and the fact that each questionnaire was personalised, having the child's first name inserted into each question throughout, was identified by the women as a positive feature, and for some was the motivation to complete the questionnaire:

"I was very impressed with the Magpie study because it felt personalised. Like when you sent the questionnaires out it had mine and baby's name on. I thought there could be so many thousands of women on this trial and you have got mine and baby's name on it. Then you sent cards thanking and everything. So I found that a worthwhile study. I found it good to have ongoing research. What made me do it was because it was personalised. Like I said to my husband there are thousands of women on this trial yet they have got my name and baby's name and they always refer to us by name.

That's what made me do it. Kind research, it is personalised, that's what made me do it. If it is a very clinical letter which some of them can be, I think I would have just put it in the bin. I was very impressed with the Magpie study because it felt personalised." [11 P/N def yes]

"I think the letters are actually Dear *[name]* which is quite nice. Someone has taken time to remember. I filled out the assessment and that was personalised to me and [*baby*], that was quite a shock, as we did not expect to get anything two years later. That is why I am happy to carry on talking about it." [06 A/N def yes]

"The questions were put in a way that they made you understand more. It gave details and information to ring this number and was very helpful. The questionnaire was set out and I understood they had kept it simple and not hard." [16 A/N def yes]

"I had to sit and think it [*the questionnaire*]. I remember sitting and thinking there are a couple of things I did not know if she could do so had to sit her down over the weekend and try and fill that section out. Things you probably have not taken much notice of. It was quite nice actually because it made me realise how developed she was. It was a positive experience. I listened to what she was saying to see if she said 'I' or 'mine', stuff like that, and the difference between filling the questionnaire and then you *[RS]* coming and doing was a progression to make sure she was developing. I got various correspondence as the trial progressed. It was quite nice it made it a bit more personal. It is nice to know what is happening afterwards. I got the result and the article and that so that was nice." [06 A/N def yes]

The women also talked favorably about the experience of the home visit, mostly for the same reasons as for the questionnaire; it gave women reassurance that their child was developing well and also provided them with additional information of their child's ability:

"I found it interesting being part of the study. I enjoyed the assessment that was done on baby that was interesting. Everyone likes to talk about their

children and themselves so that is fine by me, so it was fine." [27 A/N prob yes]

"It's nice to have a follow-up study, to talk to someone who actually knew about the trial and to find out what happened after the trial. I thought it was good. It was interesting. It is more than they do with the health visitor. I found it quite interesting. It was nice to have a follow-up. To see how they were all developing." [20 P/N not answered]

"When we met last time *[RS]* it was more helpful to me about the baby, it was seeing so much he could do. It was nice for someone else to come in take control of my child and for me to watch. It was excellent, I really enjoyed that." [39 A/N prob yes]

"I just wanted to make sure she was normal. There is not any 'normal' really, but that she was doing all right. I was quite happy. She done a few things I did not know she could do." [06 A/N def yes]

"I was not expecting it *[home visit]*. I expected a letter but not that. I thought it was interesting about [*baby*] when you *[RS]* came out, like she can jump etc. You have kept in contact and told me how things have gone on. You have not left me in the dark. It has been nice to get a letter occasionally and find out what is going on and that you have helped." [18 A/N def yes]

8.4 Conclusion

This chapter has given an insight into the long-term experiences of women recruited to the Magpie Trial. Receiving the trial results was accepted positively overall. The women interviewed thought that participants should be provided with trial results. The results explained there was no apparent harm from joining the trial. This no doubt influenced their response. It is probable also that the women's responses to receiving the results were heavily influenced by their and their child's current healthy status. However I cannot comment on what their reaction would have been, had there been a problem. Although some women could not recall the detail of the information provided in the results summary, the act of getting them was positively received. For others they found the results interesting to read, many had wondered about

the outcome, and some had even gone to the effort of obtaining the full journal publication. Some considered provision of results to those joining trials should be a routine procedure. Many understood from reading the results the Magpie Trial was a success and with that came personal pleasure of being involved. Many appreciated receiving the results for reasons other than being informed about trial's main findings. For example they appreciated they had made a contribution to research, as a consequence they were more likely to participate in future research and for some receiving the results gave them closure.

Contacting the women some years later for follow up does have the potential to cause worry. Overwhelmingly, however, the women interviewed welcomed being involved in the follow up study. Often for reasons similar to those expressed in relation to receiving the trials results, feeling valued and important to do. Additionally the follow up gave them reassurances about their child's development and an opportunity to ask unanswered questions about the trial and pre-eclampsia generally.

Chapter 9

Discussion, conclusions and recommendations

9.1 Introduction

In this final chapter I discuss and summarise the study findings in relation to the identified aims. Focus is placed on the issues taken into account by the women when considering joining the Magpie Trial. The background influences and the impact pre-eclampsia had on their decision-making experience are also given attention. The methodological limitations of the study and the consequences these may have had on the study findings are considered. Consideration is also given to the implications of my findings for future research and practice.

To my knowledge the QUOTE Study is the first formal assessment of women's views and experiences of participating in a perinatal trial while experiencing a pregnancy related illness. Two contrasting data collection methodologies were employed, each possessing its own advantages and weaknesses. The data generated from the postal questionnaire used in the Magpie follow up study allowed me to examine the views of large numbers of women throughout the UK. The co-ordinating centre for the Magpie Trial centrally handled the co-ordination and delivery of the postal questionnaires. The extensive effort by the study co-ordinators in intensive follow up resulted in an 81% (n=619) response rate allowing me to have confidence in the generalisability of the findings. In order to obtain in-depth accounts of women's experiences of joining Magpie, I conducted semi-structured interviews with 40 of these women.

The postal questionnaires and semi-structured interviews together were effective in gaining insight into women's attitudes and firsthand experience of research. It is important to note that I have integrated the two data sets at both the analysis and interpretation phases of the study, rather than presenting a formal comparison. Substantial integration, linking the findings and bringing them together has allowed for corroboration and strengthened

the conclusions of the study. When I reviewed the data obtained from the differing data collection methods independently, I found strong evidence of general agreement between opinions expressed in the postal questionnaire and those expressed by the women in the interviews. The semi-structured interviews allowed for much further consideration of themes and concepts identified from the postal questionnaires. My understanding of the quantitative findings has been substantially enhanced by the virtue of the fact that I also had qualitative data.

The findings from the QUOTE Study represent the views and experiences of the women who remained in the Magpie Trial and its follow up study for periods of 2 to 4 years. Thus, these results are, in general, a profile of those who were likely to be sufficiently satisfied with their initial experience of trial participation to remain in the follow up study. There was no observation of the actual consent process, so neither the information conveyed to each woman nor the interactions involved were accessible. It is worth noting also that the responses by the women regarding their participation in Magpie may reflect things learned about since rather than at the time of deciding to participate.

Throughout the interviews it was apparent the women's responses were sometimes contradictory. It is also important to acknowledge that all the women interviewed were in good health, as were their children, with the exception of two; one had severe cerebral palsy (woman's code: 10 A/N prob no), the other had Downs Syndrome (woman's code: 28 P/N prob yes). The women's recollections of their experiences of Magpie were almost certainly influenced by their and their child's present health. The "halo effect" described by Seguin and colleagues (1989) may have influenced women's perceptions of their experiences: a healthy baby may compensate for any personal discomfort endured and any reservations felt about taking part in Magpie. Had the women and children's health outcomes not been as good, their accounts might have been different.

Women recruited to the Magpie Trial were experiencing a serious life-threatening situation. Therefore the physical seriousness of pre-eclampsia for the woman is one that creates considerable psychological stress and anxiety about her own health and that of her unborn child. It follows then that those recruited to the Magpie Trial were experiencing psychological stress when considering participation.

9.2 What is already known about this topic

Despite the potential benefits of conducting research around the management of pregnancy and childbirth (Enkin et al 2000) and acknowledgement of the importance of doing research *with* women as participants, rather than doing research *on* women (Renfrew and McCandlish 1992:81, AIMS/NCT/MA 1997) reviewing the literature relating to pregnant women's experiences of participating in trials confirms there is still little evaluation of the impact of taking part in a trial. Given that conducting research within the maternity services has become the accepted norm in many units in the UK and women may be approached to participate in as many as five research studies during the course of their pregnancy (Baker 2005), there have been relatively few attempts at rigorously evaluating pregnant women's experiences of joining trials.

A growing body of work has pointed to the potential for using qualitative research methods to assess the perspectives of trial participants. The literature search identified thirteen reports of ten empirical studies that evaluated the short-term consequences of joining trials whilst pregnant. The studies were predominately UK based (n=5) (Elbourne 1987, Mohanna and Tunna 1999, Ferguson 2000, Kenyon and Dixon-Woods 2004, [Kenyon et al 2006, Dixon-Woods et al 2006], Baker et al 2005) and North American (n=4) (Weston et 1997, Dorantes et al 2000, Rodger et al 2003, McLeod et al 2004); one study was performed in Australia (East and Colditz 1996 [East et al 2006]).

There were few similarities in the situations of the women included in these ten empirical studies with those women recruited to the Magpie Trial in the

UK. None of the ten explored the views of women being faced with trial participation while experiencing a pregnancy related illness, in particular in the perinatal period. The studies identified in the literature explored some aspect of trial participation either in the antenatal period (Elbourne 1987, Weston et al 1997, Rodger et al 2003, McLeod et al 2004, Baker et al 2005) or intrapartum (Mohanna and Tunna 1999, Dorantes et al 2000, Ferguson 2000, Kenyon and Dixon-Woods 2004, [Kenyon et al 2006, Dixon-Woods et al 2006], East and Colditz 1996 [East et al 2006]) and therefore none could be directly related to the circumstances of women joining the Magpie Trial. Little guidance, therefore, can be drawn from the studies identified, given the characteristics of the women and their circumstances at the time.

Most information gained from the empirical studies related to participants' reasons for agreeing to and declining trial participation (Mohanna and Tunna 1994, Dorantes et al 2000, Baker et al 2005); or their understanding of trial information (Kenyon and Dixon-Woods 2004, Kenyon et al 2006). The studies conclude that the most important factors on a woman's decision to consent are related to personal benefit. When women are asked to participate in research while pregnant, benefit to themselves or their unborn baby feature as the most important considerations. Altruism is just one of the many factors.

Two studies took the opportunity to explore women's general views of taking part in research while questioning them about aspects of the research intervention; being involved in a study of having access to and holding their own obstetric records (Elbourne 1987) and experiencing fetal intrapartum oxygen saturation monitoring (East and Colditz 1996, East et al 2006). One empirical study (Dixon-Woods et al 2006) explored participants' reactions to receiving the trial results. However, pregnant women's understanding and acceptance of research methods used within randomised trials did not feature in these research studies or within the debate.

The literature gave some insight into trial participants' understanding of trial information. When investigating the quality of the informed consent process it

has been identified that participants often have misunderstandings about trials and understanding can vary between participants (Ferguson 2000, Roger et al 2003, Kenyon and Dixon-Woods 2004). Major deficiencies in comprehension include not being aware of the potential risk associated with the intervention, the unproven nature of the treatment and the uncertainty of benefit to self (Ferguson 2000, Rodger et al 2003, Kenyon et al 2006).

In three of the studies (Weston et al 1997, Rodger et al 2003, McLeod et al 2004), the findings were based on hypothetical data. The studies explored pregnant women's assessment of trial information with the view to participating in a hypothetical trial. The focus of these studies was to explore the nature of trial information, in order to improve trial recruitment (Weston et al 1997) and to determine pregnant women's likelihood of joining a proposed trial (Rodger et al 2003, McLeod et al 2004). There are obvious limitations to this type of research as it does not capture the real-life situation. Anxiety is a significant influence in decision-making, and studies have shown that anxiety is increased when participants are asked to take part in real-life research (Dorantes et al 2000). Therefore if participants are asked to base their decisions on being in a hypothetical versus an actual trial, anxiety levels may be quite different, and so too may their decisions. As a potential trial participant it can be difficult to imagine how one might react when faced with joining a trial, especially if the situation is unfamiliar and unreal.

The research studies evaluated were mostly small in scale, with the exception of the postal questionnaire study (n= 1875) by Kenyon and Dixon-Woods (2004), and therefore restricted in terms of providing any major guidance as to what are the most important issues to pregnant women when joining a trial. Five of the studies (Mohanna and Tunna 1999, Ferguson 2000, Rodger et al 2003, Baker et al 2005, Kenyon et al 2006 [Dixon-Woods et al 2006]) explored women's experiences of participation using face-to-face interviews. These studies have only identified 69 women as having been interviewed in-depth about their trial experiences: Mohanna and Tunna (1999) n= 18, Ferguson (2002) n=26, Kenyon et al (2006) [Dixon-Woods et al 2006] n=20 and Baker et al (2005) n=5.

Kenyon and Dixon-Woods (2004), in their questionnaire survey examining the understanding of trial information, acknowledged the limitations of using a questionnaire for data collection. The method chosen did not allow the researcher to ask for clarification nor the woman the opportunity to respond to questions not included. It was also difficult to judge the extent to which written responses represent difficulties in written expression. In addition, although the response rate was acceptable for a study of this type (61%), a considerable proportion of women did not respond.

The general discussions identified in the literature were mostly from the perspectives of researchers, although there were three accounts from trial participants themselves (Moran 1993, Washington 1995, Sudlow 2005), which related to the ethical difficulty of recruiting pregnant women into trials. This discussion was concerned with the difficulties a woman may experience when needing to consent to research while in the labour and therefore under stress and possibly in pain. Informing women antenatally (Robinson 1997a, Robinson 1997b, Spencer and Dawson 2004) seems an appropriate solution, and it is currently recommended (AIMS/NCT/MA 1997) that women should not be approached to consent to participate in perinatal research unless they have been informed about it earlier in their pregnancy. However, the benefits of providing perinatal trial information early in pregnancy have not been confirmed (Hundley and Cheyne 2003, Iltis 2006, Vernon et al 2006).

The literature identified there is limited understanding and evidence about the provision of trial results to participants. While government initiatives, users, and research ethics committees are generally supportive of the concept, the needs and attitudes of participants are relatively unknown. To date, there is little published evidence to suggest either positive or negative outcomes of providing perinatal trial results.

Areas identified as needing to be addressed were therefore: participants' understanding of the purpose of the research, their views about the nature of research, their reasons for joining, whether any pressure to join was experienced, the involvement of others in decision-making, and evaluation of

understanding of written and oral information provided at the time of recruitment. The issues of understanding of trial methodology, in particular the concepts of equipoise, randomisation, and blinding, needed further exploration also. Despite being particularly valuable for development of future randomised trials, there had been relatively little direct research on participants' views of perinatal trials. The literature review has revealed that these questions had yet to be formally addressed from the perspective of pregnant women. This was an important omission in the literature that the QUOTE Study hoped to address.

In conclusion, the literature acknowledged exploring trial participants' views of the research process is vital in order to improve the quality of trials and the trial experience for those taking part. Participants can give valuable insights into the research process; and ultimately having high quality evidence about the experiences of being in a trial will give a greater understanding of how trials are perceived by participants and so improve their design and running. Reviewing the published literature confirmed there was no empirical research relating directly to the circumstances experienced by those recruited to the Magpie Trial, and although the issue of pregnant women participating in clinical trials has been identified as requiring particular attention (Hundley and Cheyne 2003) there remains little work specifically exploring trial participation from the pregnant woman's viewpoint. I therefore needed to look beyond the confines of pregnancy in order to learn more about trial experience from the participant's perspective. Other areas of health, although not directly transferable, did provide useful illustrations of the trial participants experience. Extending the review of the literature provided further understanding of the more generic issues relating to participating in clinical research that was necessary in order to fully understand this subject.

Highlights of this literature are summarised in the box below:

What is already known about this topic

- Few empirical studies have explored the views of women joining perinatal trials. It is not clear how women experiencing pregnancy related illnesses feel about participating in clinical trials

- A current recommendation is that women should not be asked to consent to take part in perinatal research unless they have been given written information about it during pregnancy. However, the benefits of providing information in the antenatal period about perinatal trials have yet to be confirmed

- Benefit to the mother herself or the baby are key motives for participating in perinatal research; and appear more important motivations than altruism.

- Participants' understanding of the purpose and design of trials is often suboptimal by researchers' standards. Trial practices including randomisation, placebo and blinding are poorly understood

- Women appear to want to be informed about trial results; however, there is little evidence about the optimal methods for disseminating the results; or of the implications of doing so.

9.3 What the QUOTE Study adds

Although large numbers of pregnant women have participated in clinical trials, little is known about how they experience the informed consent process in the perinatal situation. QUOTE is, to my knowledge, the first empirical assessment of women's views and experiences of participating in a perinatal trial while experiencing pre-eclampsia. Women's perceptions and recall of their experiences of participating in Magpie were understandably entwined with their overall birth experience. Their responses to participation were

positioned in the context of their individual childbirth experiences and the health care they received. Many women entering Magpie, although not in an acute emergency situation, were experiencing a dangerous and frightening condition. A frequent characteristic of pre-eclampsia is that women become acutely ill without much warning; and though those with mild pre-eclampsia often feel relatively well, women with severe pre-eclampsia may experience headaches, visual disturbances, epigastric or right upper quadrant pain, nausea, and vomiting or rapidly progressing oedema, symptoms developing in what appears to be a very short period of time. The unpredictability and speed at which pre-eclampsia can develop and the fact that most women have little prior understanding of the condition causes additional anxiety.

Due to the life-threatening potential of severe pre-eclampsia, most women on the Magpie Trial were cared for on an obstetric high dependency unit. As a third of eclamptic fits occur postpartum, intensive monitoring was often continued for 48 hours after delivery. The conditions for acquiring informed consent were therefore very far from ideal, with many women were in discomfort and anxious at the time consent was required. Furthermore, only a limited amount of time was available for the informed consent process since most women needed immediate medical treatment. A special dilemma exists in obtaining informed consent in perinatal trials due to the fact that for many the implications for an unborn baby also require consideration. Not surprisingly, the various enrolment procedures used in perinatal trials reflect a growing controversy over whether informed consent can and should be obtained under these particular circumstances. Previous research findings, already discussed, are not fully generalisable to the particular experiences of this group of women for whom the nature of the trial experience was relatively unknown and therefore needed to be formally addressed. Informed consent in this situation was potentially very difficult.

9.3.1 Further evidence regarding amount and timing of information

During the interviews the women described the time of recruitment as immensely frightening, stressful, and for some very traumatic. Much of this was related to the unexpected and sudden occurrence of severe pre-

eclampsia, the clinical situation unquestionably contributing to what for some was already a difficult decision-making process. It is clear from the women's accounts that the time taken to consider joining Magpie was heavily influenced by the limited time available. Women were actively encouraged to make their decision to join Magpie as quickly as possible as the seriousness of pre-eclampsia meant treatment could not be delayed. From most of the accounts, it was evident that the fear they were experiencing both for themselves and their baby contributed to the speed of their decision. Most had a clear understanding of the desperate situation they were in and the limited time available to decide. Others decided quickly because they were approached in labour or just after delivery and were unable to give the information lengthy consideration and therefore agreed in a short space of time. Many commented on how hurried the whole situation felt; and only one woman felt able to tell the clinicians she needed more time to reach her decision. For some women, however, it appeared the decision was quick because of its ease. The decision appeared casual even, a decision that was not particularly agonised over.

Among those women who took more time to decide this too was driven by circumstance, because time *was* available. Being informed about Magpie whilst admitted for observation on the antenatal ward (and therefore only potentially eligible) gave one woman a period of time to consider participating. However, she too felt some urgency to join because of the daily approach by the recruiting midwife, until a decision was made. Other women appeared to either be in a less stressful situation or were less stressed by the approach used. These women were spoken to in what appeared to be a much more relaxed way and were given time to consider the trial. Some clinicians left the room in order for the woman and her family to deliberate privately. Trusting the clinician not to offer anything that would be detrimental to either themselves or their baby also seemed key to the time taken to consider for all the women.

For the women the onset of their pre-eclampsia was not predicted and most were admitted to hospital with little warning. Many had little understanding of

their condition, adding further to their anxiety. For the majority clinicians provided information about Magpie at the time of eligibility and not before. The clinicians were unable to identify who would and would not be affected by the condition in advance, so the provision and timing of information about possible treatments and potential clinical trials related to pre-eclampsia was challenging. Although the majority of women were reasonably satisfied with the level of detail of information received, it was evident the timing was problematic. Most indicated that had they been told earlier in their pregnancy they would have found the decision to join less stressful. However, some said they would not have wanted to know about the trial early and made comments to the effect that knowing about the trial before eligible would have caused them unnecessary worry.

These findings from QUOTE were similar to the findings by Mohanna and Tunna (1999) in their study of pregnant women's decisions to withhold consent to a preterm labour trial. In that, most of the women had not considered they were at risk of preterm labour and therefore could not see the relevance of being told early about the trial. Vernon et al (2006) have outlined how informing women early in pregnancy can bring about tension between promoting pregnancy and labour as a normal physiological process and the possibility of experiencing an adverse event. The chance of experiencing an adverse event is generally very small and to present women with a detailed argument around each possible complication can unnecessarily detract from the normality of pregnancy.

The need for elaboration of information is highly individual. It was apparent in QUOTE that it was dependent on stress, prior knowledge of Magpie and pre-eclampsia and the severity of pre-eclampsia experienced. Many women emphasised the need for repetition as well as details to be described in lay terms. Additionally, QUOTE highlighted that women frequently lacked a full grasp of the differences between the Magpie Trial and standard clinical practice, highlighting that the consent process should have included particular attention to the distinctions between procedures performed as part of research and those performed as part of standard clinical practice. The

continuous consent approach to obtaining informed consent for research has been proposed (Allmark and Mason 2006) as a method for solving these difficulties; by giving information at more than one point in a trial participants will assimilate the information much better.

9.3.2 Self-interest is a key motive for participating

Research participants in randomised trials often believe that participation will result in better treatment, as do researchers. The findings from the QUOTE Study are consistent with this as the majority of women agreed to participate in Magpie primarily because they believed participation would result in benefit to either themselves or their baby. Major motivating factors for participation fell into three broad categories: self-benefit (trial might help treat pre-eclampsia), benefit to their child (treatment may minimise the associated risks of pre-eclampsia to the unborn baby) and altruism (help future women or for the good of medical science). In most cases, women identified more than one benefit; just five of the 40 women interviewed identified altruism exclusively as their reason for taking part.

The majority of women expressed a preference for the active drug, magnesium sulphate, and very few voiced concerns about any possibility of risk to either themselves or their unborn baby. In a number of accounts it appeared the recruiting clinician had expressed the hope that the woman would be randomised to magnesium sulphate, because they were already convinced of its benefit (as previously discussed Chapter 2:56). This finding of lack of personal equipoise by recruiting clinicians supports the results of other studies, and is perhaps not surprising given that a fundamental ethical perception of research is that the well-being of an individual must never be sacrificed for some perceived greater collective good. Appreciating the clinicians' lack of clinical equipoise meant some women had little difficulty in deciding to join, Magpie offering them the opportunity of receiving benefit. Of those women randomised to placebo, the majority believed they had been randomised to magnesium sulphate. Had Magpie not been a double–blind trial, and had those randomised to placebo been aware of their allocation, some might subsequently have withdrawn from participation.

Participation therefore gave many women the possibility of receiving what many clinicians, and consequently women themselves, thought to be an effective and 'proven' treatment and therefore the preferred option. It is worth noting that the Magpie Trial information leaflet, which was given to women, reflected both medical opinion and practice at the time, stating: "Some doctors give magnesium sulphate to women with pre-eclampsia, hoping that it will stop them having a fit and prevent some of the other problems of pre-eclampsia. There is very little useful research into whether magnesium sulphate really is the best treatment. Although one study has suggested that it might be good for women, this was not conclusive and gave very little information about the effects for the baby" (Appendix 16).

9.3.3 Trust in the clinician is key to participation

Trust in the clinicians was another important element in the recruitment decision. Some women relied on the confidence they had in the recruiting clinician: trusting that they would not expose them or their babies to anything risky. Health professionals involved in Magpie had dual roles: as clinician and as researcher. As clinicians, their objective was to apply existing knowledge for the best possible outcome of each woman. As researchers their objective was to gain further knowledge for the greater good and in the case of Magpie to leave some treatment decisions (administration of magnesium sulphate) to a chance process. In this type of situation care and research are so closely interlinked that it is often impractical and impossible not to intermingle the two. Women may have expected their obstetrician or midwife to have acted first as clinicians whose primary concern was their physical well-being and care. The clinicians' dual role as researcher may have appeared irrelevant to the clinical decision to be made.

Those having trust in their clinician were drawing on their general understanding of healthcare and health professionals as well as their personal experience; most joined Magpie towards the end of their pregnancy and therefore had already developed a relationship with their healthcare professionals, even though this relationship of trust has been described as an unequal one (Kitzinger et al 1990:97). Trust in the clinician seemed critical to

women's agreement. Decisions about childbirth may be seen as different to other health-care decisions; but at the time of recruitment to Magpie the women involved were unwell, extremely vulnerable and therefore particularly dependent on and influenced by their clinician.

The decision to join was also influenced by the exchanges between the women and the clinicians at time of recruitment. Some women appeared to form close attachments with the staff in what would appear a very short period of time. Many expressed that they felt safe and reassured by the fact that the midwife was always in the room with them. The attitudes and behaviour of the clinicians towards the women appeared to be a factor influencing recruitment, perhaps reflecting the women's expectations that their clinician would always act in their best interest, (even when the clinician explained that treatment in the Magpie Trial was randomised). Women frequently expressed the view that magnesium sulphate would not be offered if it did not carry a strong potential for benefit, many understanding that the trial would not be performed if it was thought to cause any significant risk.

Although some women sought the opinion of family members and friends, it was apparent they had little involvement or influence on the woman's decision. Many women emphasised that their partner played a role in providing a second opinion, as someone to confer with. However, women dismissed the idea that their family were in the position to influence their decision; either because they were distressed too, or were not able to interpret trial details any better than the women themselves. Most women said they made the decision to join independently; and the family being present was neither required nor a substantial influence.

Although most women appreciated the blinded nature of the trial and therefore understood the clinician could not tell them to which group they had been randomised to, there was a clear sense that clinicians were in part able to deduce (because of side effects) who had been randomised to magnesium sulphate and who not. Women reported that when the clinician thought she had been randomised to magnesium sulphate, this was often associated with

an expression of satisfaction or relief. This in turn gave the women further confirmation of the (unknown) proven benefits of magnesium sulphate, and consequently validated their decision to join. When asked in the QUOTE Study interview to guess trial allocation: most women thought they had been randomised magnesium sulphate (n= 22 [17 guessing correctly]), 11 did not know, and 7 thought they had received placebo [5 guessing correctly]. Thus, although appreciating they could have been randomised to the control group few women (n=7) actually thought they had been.

Some women felt that being randomised to placebo would involve additional risks, because it would involve not taking an active treatment they perceived to be beneficial. For others there was an appreciation, and with that reassurance, that had they been randomised to placebo and subsequently had an eclamptic fit they understood they would be treated with magnesium sulphate. The corollary of this was to reduce any concern about risk and reinforce the impression that there was no choice about whether to participate - the women ultimately seemed to feel that by participating they could not be disadvantaged. Despite being given the Magpie Trial information leaflet many women did not seem to have any knowledge of the potential risks involved. Some women did not recall being informed of risks, some said they were explicitly told that there were none, others did not recall being given the information leaflet. Some said that they gave consent only because they believed that the treatment would not harm their baby.

In addition to perceived benefits at the point of randomisation women also mentioned there were other supplementary benefits from participating in Magpie. Women perceived they received more information about pre-eclampsia as a result of participating in Magpie. The most frequently mentioned was the perceived guarantee of better care that resulted from the increased clinician surveillance, receipt of additional clinical monitoring, and physical examinations, as well as follow up. The emotional advantage of having one-to-one care was also mentioned. Being given additional information about pre-eclampsia and therefore feeling better educated was also highlighted. A perception of benefit to their physical condition, such as

lowering the blood pressure and a general feeling of wellbeing as a result of being on the trial was also identified. Other benefits mentioned less frequently in the interviews were the psychological benefits of increased interaction with clinical and research staff, and a sense of feeling important.

Most women recruited to Magpie perceived magnesium sulphate to be beneficial to them at the time of recruitment. They did not always appreciate that there was uncertainty over the favourable effects of magnesium sulphate and the possibility of receiving a potentially beneficial therapy was promising. Women frequently expressed the view that the research would not be being done if it did not carry some promise of benefit, and alternatively many assumed the intervention would not be done if it posed significant risks. The apparent lack of uncertainty on the part of clinicians involved seemed to cause poor appreciation among the women of the unproven nature of the trial treatment, which in turn seemed key to their decision-making. Collaborating hospitals did not administer magnesium sulphate for pre-eclampsia outside the confines of the Magpie Trial: participation was therefore in the main seen as a vehicle to receiving a preferred beneficial treatment that was not routinely available. Getting 'ideal' treatment by going into the trial was therefore preferred to no chance of getting it. Women also joined in the hope of trying anything because their condition was life threatening, so they had nothing to lose and everything to gain.

Accounts by the women relating to the consent process suggested that some clinicians, albeit unintentionally and indirectly, promoted the use of magnesium sulphate as safe, by speaking openly about its widespread use in other parts of the world. Women understood this to mean that the beneficial effects of magnesium sulphate had already been proven, the risk was negligent, and Magpie was simply providing evidence for clinicians in the UK to use the drug routinely. Faced with the possibility of having an eclamptic convulsion and seeing Magpie as a way in which this might be prevented, the decision to take part therefore seemed logical and straightforward. Agreeing to research eagerly in the hope of accessing a potentially beneficial

intervention has been termed "instinctive consent" (Snowdon et al 2006). This can be seen clearly amongst the women in the QUOTE Study.

Although the women appreciated the voluntary nature of the trial, clinicians, especially those clinicians that were not in personal equipoise, (previously discussed, Chapter 2: 56), may have 'unwittingly coerced' them (Little 2002) by their own personal preferences. It appeared there was some suggestion from the women's accounts that some clinicians were not in personal equipoise regarding the use of magnesium sulphate for the treatment of pre-eclampsia. The language or behaviour used by clinicians, even if subtle or not intended, this may have influenced the women to believe that Magpie offered them the opportunity to receive greater benefit. Women likely assumed that their obstetrician or midwife were acting first and foremost as clinicians whose primary concern was the woman's health. In the context of Magpie, the emergency situation itself is 'coercive'.

Women's descriptions of their reasons for participating in Magpie and of various forms of pressure experienced in connection with the consent process were considered, to establish to what degree their decision was voluntary. Women were evidently influenced by the clinicians to consent to the trial, especially by those with a strong belief in the benefit of magnesium sulphate. The other forms of pressure that the women experienced were mainly attributable to the emergency situation caused by having severe pre-eclampsia. Clinicians emphasised the limited options available and as a consequence many women were keen to receive treatment as soon as possible.

9.3.4 Distinction between research and routine clinical care can be unclear for trial participants'

It was not possible, nor was it the focus of this study to examine whether or not the women fulfilled certain criteria of competence at the time they gave consent to the Magpie Trial. It was possible, however, to analyse how the women described their ability to understand, reason, communicate and come

to a decision at the time of recruitment. As I was not present when consent was obtained, this is an evaluation of the women's perceptions of their understanding of what they were told, which is not necessarily the same as what they were actually told. The quality of the information they were given has not been assessed, but rather their judgment of it and the degree to which they felt they had understood it. Regardless of whether the women's recollections were 'accurate', it was their satisfaction that was the key issue in this study; even so, issues of informed consent do emerge.

Women were given the Magpie Trial information leaflet (Appendix 16) as part of the consent procedure. Clinicians expanded on this written information by providing additional oral information at the time of recruitment. The content of the additional information was dependent on the individual recruiting clinician and therefore was not consistent or standardised. Written information was helpful in the decision-making process, but for only a few of the women interviewed. Some women were not capable of reading it because of the stressful emergency context they found themselves in. Others claimed that they read the information, but the detail was difficult to take in due to the situation, for some it was because they were in labour at the time. There were a few women who did not remember whether they read the information sheet prior to or after giving consent and a few could not recall receiving any information sheet at all.

It appeared that trial information provided orally was the most essential source. Nevertheless when the women were asked about details, they often had significant gaps in their knowledge about the trial. These included not being aware of the unproven nature of trial treatment, and the potential for increased risk or discomfort, and certain aspects of design used in randomised controlled trials. Some women did not appreciate the uncertainty of benefit to self.

Most women were able to describe some aspect of the concept of randomisation, particularly in terms of the involvement of chance, with some

having more detailed understanding of treatment comparisons, concealed allocation and experimental design. Despite being able to recall the involvement of chance in their allocation, the same women indicated that they expected to receive the experimental trial treatment (magnesium sulphate). While most women in the QUOTE Study did not appear to appreciate completely the concept of randomisation they did acknowledge it was a rational and reasonable way of testing treatments.

There were a number of other factors contributing to the women's acceptance of randomisation. Women were aware that they would ultimately receive magnesium sulphate if they needed it, for example if experiencing an eclamptic convulsion. As a result women assumed that by joining Magpie they were not going to be put at risk or denied treatment if required. This understanding that magnesium sulphate could be administered outside the confines of the trial proved crucial in determining whether women were satisfied with the concept of randomisation and accepted the resultant treatment allocation. The finding that the women were often influenced by their understanding that the 'experimental' trial treatment was not a new drug (frequently used outside the UK for pre-eclampsia) and had been previously tested in the UK and found to be useful and safe (for women with eclampsia) was also of importance. It contributed to them being able to consider participation as a low-risk undertaking. Women who had some knowledge about possible risk, also had immense trust in their clinician, to the point where assumptions of no risk were made when in fact no knowledge was actually present. This perception of no risk reinforced the view that randomisation was relatively uncomplicated, rational and for most not an issue.

Literature relating to equipoise, as previously discussed (Chapter 2:56), has focused almost entirely on clinicians' perceptions, demonstrating the existence (or not) of two types: collective and personal (Freedman 1987). The QUOTE findings suggest that most women supposed that some clinicians perceived the trial treatment to be beneficial. This supports the widespread and unproven belief that new treatments are likely to be superior

to existing alternatives (Chalmers 2004, Chalmers and Matthews 2006). This apparent lack of uncertainty on the part of clinicians seemed to create a poor appreciation among the women of the unproven nature of the trial treatment, which seemed key to their decision-making. It appeared this fundamental principle of trial design was not part of the discussion at the time of trial recruitment. In attempting to make sense of their participation in Magpie, women produced accounts that on the one hand described their understanding of the fundamentals of equipoise, but on the other hand challenged these understandings, for example, by stating that they joined Magpie in order to receive a beneficial treatment (magnesium sulphate). Given the suggestion that trialists often have treatment preferences, it could be argued that the women's views were accurate as their accounts reflected the opinions given to them by the recruiting clinicians. It is important to note the women in QUOTE did not voice concerns about wanting additional explanations about the methodology used in the Magpie Trial or the uncertainty or experimental nature of it. Women did emphasise the need for clarity and simplicity of the explanation as well as an unhurried discussion and time to consider their decision.

Despite some positive elements of the recruitment process from the women's viewpoint, it appeared some women were not fully satisfied with the information they received about the trial. Although most dissatisfaction related to the clinical situation they found themselves in and the need for a quick decision, women did indicate trial information provision in parts was inadequate. Women made a distinction between the way information should be provided and the content of the information. Remarks provided some insight into the issues that were important to them at the time of recruitment. In-depth information about the trial including the trial procedures was requested. Information about the possibility of side effects and possible harm caused by magnesium sulphate (with particular emphasis on the baby) were requested most often at recruitment. Since joining the trial some of the women had requested un-blinding of treatment allocation.

As previously discussed women were asked to consider joining Magpie at a difficult and highly stressful time. Their understanding of the trial was primarily derived from the consultation process, rather than the information leaflet. Women's knowledge varied widely, and for most, their comprehension could be considered limited. Many factors could potentially influence this. While it is not possible to determine to what extent misconceptions were due to lack of a understanding on behalf of the women or a lack of communication skills on the part of the clinicians, it is evident that the clinical context affected their ability to concentrate. The fact that the symptoms and severity of pre-eclampsia can vary considerably may explain why some women felt fully competent to decide while others clearly did not. Most women had limited understanding of pre-eclampsia prior to the Magpie Trial and the difficulty in understanding complex medical arguments put to them at a time of stress was evident.

Despite this, when asked in the qualitative interviews, nearly all women were happy with their decision to participate and reported that they would join the study again if in the same circumstances. Data from the postal questionnaire confirmed this; a total of 525 (85%) of women said that they would participate again. The main reasons given for agreeing to participate again were potential for self-benefit and altruism. Few (15%) reported that they would decline or were not sure what their decision would be. The main reason they gave for thinking they would decline if asked again was due to the side effects they had experienced. Furthermore, while there were noticeable flaws in their knowledge and many could not recall some aspects of Magpie, the women had no regrets and felt generally satisfied with their experience and that they understood Magpie well.

Assessing the information needs of trial participants can be difficult. Deciding how much information needs to be supplied to research participants for consent to be truly informed has previously been identified as controversial, especially as participants can have widely differing preferences for the type, amount and format of information they receive. Existing research frameworks offer guidance about what constitutes necessary information for an informed

consent (WMA 2004). Essential information includes not only that about the nature and purpose of the research, but also the relevant balance between possible risks and benefits, and information about the implications of participation, including that the study is voluntary and that failure to consent will not jeopardise clinical care. Information about relevant methodological issues should also be included as appropriate; for example participation in a randomised controlled trial should be preceded by explanation of such concepts as randomisation, blinding, and equipoise.

This requirement is an ideal, however, and does not necessarily reflect real life situations, nor acknowledge what may or may not be feasible. It is important to recognise the importance of the particular circumstances under which information is provided. When the declaration of Helsinki was formulated, Bradford Hill (1963), an innovator in clinical trials, claimed that there is no one way of doing clinical trials ethically and giving detailed advice; and if there were this would harm both research and ethics. He argued that ethical judgements have to take into allowance the specific circumstances of each trial (Bradford Hill 1963). Comments made by the women in the Magpie Trial suggested they were somehow unclear or unaware of what was happening, or felt too anxious to be bothered about what was happening. For many women the need to get better was the overriding factor in whether they considered participating. It is not clear if providing them with a detailed explanation of the trial and the scientific method underlying a randomised controlled trial would have been helpful or desirable. Nor is it clear whether this greater understanding would have led to higher or lower levels of satisfaction and what impact such knowledge would have had on their trial experience. Too frank an explanation, with too much information is overload, and has been shown to have considerable negative consequences (Thornton 1992).

Health professionals, researchers and medical ethicists may be assessing trial participants' information needs based on their own understanding of the research process and ethics. Of course trial participants have the right to information about trial procedures before participating; nevertheless in the

situation of Magpie it would not have been possible practically to give information about every aspect of the trial. Trial participants may never know as much as trial clinicians, but the question remains do they actually need to? Even recruiting clinicians themselves rarely understand all the issues involved in a trial (Ziebland et al 2006). Moreover, with health care becoming increasingly scientific, the question is raised as to whether it reasonable to expect a layperson to have the same level of knowledge as their clinician? - especially as there is evidence that health care professionals themselves have poor understanding with some aspects of health care.

Many of the difficulties in obtaining informed consent for research for perinatal trials relate to the problem of imparting information in a stressful or sometimes emergency situation. Clinical research has become more and more technically advanced and accordingly more difficult for people outside the health professions to understand. The low levels of knowledge and understanding of research methodology in the general population compound this difficulty. In view of this it is debatable whether fully informed consent is ever obtained in its fullest sense, especially in circumstances such as those of the Magpie Trial. It has been argued that full information about clinical trials may be 'needlessly cruel', burdening participants with too much at the point of diagnosis (Tobias and Souhami 1993)

Women in the Magpie Trial reported that they were satisfied with their experience of the trial, and although sometimes lacking knowledge they felt they had sufficient understanding to make their decision. Women's self-assessment of their understanding demonstrated that most were unable to describe all aspects of the trial fully, yet the women considered themselves knowledgeable. I propose several reasons for this discrepancy between perception of and actual knowledge. First, women may not have placed too much importance on the need to recall all aspects of Magpie. They were satisfied simply to have either a positive or negative feeling towards the treatment options. Magnesium sulphate was overwhelmingly considered a positive option, although the reason for this was sometimes flawed. The gap between perceived knowledge and actual knowledge is a concern; however,

the implications of this are that researchers and clinicians need to trust trial participants to make decision they feel right for themselves, regardless of whether this is based on the researchers, clinicians or ethicists' understanding of what the trial is about. Respect for persons, including respect for their self-determination and recognition of their integral role in research is required.

9.3.5 Women appreciated being informed about the trial results

The offer to provide research results to participants at study completion is based on the principle that respect for persons should continue following study closure, to avoid treating research participants purely as a means to an end. On completion of the Magpie Trial women received a copy of the trial results and were sent as a summary by post (Appendix 6). The summary was prepared in consultation with representatives of the UK-based user group, Action on Pre-Eclampsia (APEC). It began with thanking the women and acknowledging their contribution. An overview of the Magpie Trial aimed as a reminder was provided, followed by a description of the main findings. The results summary informed the women that magnesium sulphate halves the risk of convulsions for women with pre-eclampsia and probably reduces maternal death. Magnesium sulphate, as prescribed in the trial, is safe for both mothers and babies, although unpleasant maternal side effects, particularly flushing, are common. Copies of newspaper clippings of the press releases at the time the results were launched, citations of the medical publications, and details of how to contact the trialists for further information were also provided.

Relatively little is known as to how participants receive information provided about study results and what this impact this has on their psychological well-being. During the interviews performed as part of the QUOTE Study I was able to examine the reactions to and implications of offering trial results to the participating women. One of the arguments against providing results is that research participants might not want them; however, the women's responses from both the postal questionnaires and interviews suggest otherwise.

Both methods revealed that the women appreciated being informed of the results, as many had wondered what the conclusions of the Magpie Trial were. Moreover, some women felt that by not feeding back the results to participants, researchers would not be practicing ethically or acknowledging the vital contribution research participants make. Many of the women, although surprised by the contact, did not respond negatively to knowing the results. Overwhelmingly, women stated they enjoyed reading the summary and found the additional information valuable and interesting.

The results enabled women to gain a better appreciation of Magpie as well as a good understanding of its conclusions. For some, receiving the results allowed them to have closure to their participation, completing what was a difficult time in their lives. Reading the results prompted feelings of altruism and gave satisfaction in being part of a successful trial. Many acknowledged feeling good about knowing their participation would help future mothers and babies; some even acknowledged they too could benefit one day by the research findings.

Within double-blind controlled trials sharing the results with participants may encourage them to request their individual trial treatment (un-blinding). Participants may want to understand study conclusions relevant to them and their children's health outcomes. Unblinding of treatment allocation was not provided routinely with the Magpie Trial results, women were required to request this in writing. Even after being provided with the results, few women wanted to know their unblinded treatment, only three requested it. Nor did women explore the possibility that they might have been randomised to an inferior arm of the trial (placebo) and therefore been denied of a beneficial treatment or put at risk.

Most of the women appeared to interpret the results in terms of their present situation. The women were relatively well, and the results pertained to a part of their life that had now passed. This perhaps accounts for their relative satisfaction. Had the women and their children had poor health outcomes

that could be attributed to either pre-eclampsia or magnesium sulphate they might have viewed the results differently.

A major concern in providing research results to participants is that the content may be upsetting or worrying. None of the women that returned their questionnaire or were interviewed gave any indication of detrimental effects from receiving the results. At a minimum, trial results should be offered as a reward, acknowledgement, or sign of appreciation for involvement in research. Sharing research results with participants and society in general could result in better communication between professionals and the lay public. From a researcher point of view, sharing results might lead to the public having a better understanding of clinical trials, thus increasing clinical trials accrual and ultimately leading to improvements in health care. Provision may also improve communication between investigators and participants in research, enhance the transparency of clinical research, and improve public perception of biomedical research.

9.3.6 Women welcome long-term trial follow-up

In recent years acknowledgement of the importance of long-term follow up of participants in perinatal trials has grown (American Academy of Pediatrics, Committee on Fetus and the Newborn 2002, Halliday and Ehrenkranz 2003). The importance of carrying out long-term follow up of research participants is notably supported by user groups such as AIMS (Association for Improvements in Maternity Services) who have advocated for some time that with all childbirth research the names of mothers and their babies should be kept so that long-term follow up is possible (Robinson 1994).

Little thought, however, has been given to exploring how the participants feel about being contacted some years after the event by trialists and subsequently followed up. The QUOTE Study provided an opportunity to explore in-depth how the women felt about being contacted for follow up of the Magpie Trial. Re-contacting research participants some years after randomisation does have the potential to cause apprehension. Nonetheless, the women were enthusiastic about being involved in the follow up study and

appreciated the contact. Being involved was important for a variety of reasons: it provided answers to unresolved questions about pre-eclampsia and Magpie; it meant their contribution to the trial was recognised; it gave them welcome reassurances about their child's health and development; gave them ideas as to ways of stimulating and playing with their children and also provided them with additional information of their child's abilities.

The women were often surprised by the contact, as some had given little thought to the trial since coming home from hospital; nevertheless they were still receptive to the contact. The favourable reaction from the women could be linked to how the follow up study was presented. Women found both postal questionnaires (child developmental and woman's) easy to complete; they found the child development questionnaire particularly enjoyable as well as reassuring. The format of the questionnaire and the fact that each questionnaire was personalised, was identified by the women as a positive feature, and for some was the motivation to complete it. The women also talked favourably about the experience of the home visit, mostly for the same reasons: it gave them reassurances that their child was developing well and also provided them with additional information of their child's ability.

As with the receipt of the trial results, most of the women responded to the follow up study in terms of their present situation – both they and their children were well, and the follow up study confirmed this. This may account for their satisfaction. Had the women and their children had poor health outcomes that could be linked to either pre-eclampsia or magnesium sulphate, they might have viewed the results differently. There was no evidence that the follow up study caused unwelcome distress by reviving memories of a serious illness.

Unblinding of treatment allocation was not provided routinely as part of the follow up study as the researcher performing the developmental assessments on the children was blinded to the study allocation. The visit did, however, prompt some women to want to be unblinded.

A narrative account of how the Magpie Trial follow up study was carried out (Farrell and Duley 2007), gives a further insight into the women's reactions to follow up, including those living in the UK (Smyth and Armstrong 2007). Before the follow up study began, the issue of how best to contact the families in the UK was considered, since contact could be unwelcome, especially if the mother or child was unwell. Initial contact was made therefore to the families' general practitioner to ensure a first approach would be appropriate. Families were then usually offered a home visit by telephone, which was received well.

9.3.7 Summary

Despite the widespread use of randomised controlled trials, until recently little attention has been paid to participants' reactions to and understanding of their trial experience. This study has attempted to shed some light on the Magpie Trial, as experienced by the women who participated in it. The data presented gives valuable insights into the women's views and experiences. The response rate to the postal questionnaire was excellent (81%) and has permitted reasonable confidence in the findings. The strength of this study, however, lay in its use of both quantitative and qualitative research methods, the latter to explore the women's experiences in-depth. It is important to note that the women came from a range of educational and social class backgrounds and all were able to engage well in the interviews.

Although the results suggest the need for improvements in informed consent to research, they also point to its complexity in the setting of perinatal clinical trials. The experience from QUOTE supports previous studies suggesting that the 'gold-standard' of true informed consent is difficult to achieve. The findings suggest that current official guidance regarding consent to research may be unfeasible, particularly because it requires trial information to be complex and standardisation of the process, regardless of the underlying clinical situation. The QUOTE study also identified that a process that does not recognise the particular circumstances under which decisions are made may be inadequate. Clearly, a new approach is required, which takes into

account the preferences of participants themselves, and recognises their differing needs.

Highlights of the findings from the QUOTE Study are summarised in the box below:

What the QUOTE Study adds

- This study has, for the first time, formally assessed women's views and experiences of participating in a perinatal trial whilst experiencing a pregnancy related illness (pre-eclampsia)
- There is a need for consent processes to recognise the different circumstances under which consent may be given
- Self-interest and trust in the clinician is key to participation
- Distinction between research and routine clinical care can be unclear
- Women appreciate being informed about trial results
- Women welcome long-term follow up

9.4 The QUOTE Study limitations

The following limitations of the study should be borne in mind in review of the results and their interpretation:

First, the follow up study design meant there were differences in the interval between recruitment to the Magpie Trial and the QUOTE Study interview. Timing of the interviews was dependent on women completing the follow up study postal questionnaire, as only then could they be contacted and offered an interview. For the majority this was also after their follow up study home visit. Time points therefore ranged from two years to four years and seven

months. Although it might be expected that those with the biggest gap between recruitment and interview would have greatest difficulty with recall (and there was some evidence that some key characteristics of the trial could not be recalled) no link to timing was evident. The birth of a child represents a landmark event in the lives of all involved, and for the mothers particularly, who tend to remember their birth experiences vividly and with deep emotion. Women in the QUOTE Study were being asked to recall a particularly significant episode in their lives, hence their vivid memories of their experience.

It is important to acknowledge that the views solicited come only from those women who chose to participate in the Magpie Trial; women who declined were not interviewed. The babies of all the women interviewed survived, and for most part were in good health. Had the outcomes not been as good, their thoughts might have been different; and some of the women indicated this in their interviews.

Some women gave accurate descriptions of the trial but on further questioning contradictions appeared. Throughout the interviews women were reminded to describe what they knew before recruitment, rather than what they had learnt since; however this was clearly difficult for the women sometimes to separate and overlap was evident.

Another potential limitation for the QUOTE Study was the possibility that the interviews were performed by myself the research midwife for the Magpie Trial. I recognised that some women might find it difficult to talk openly about their experiences, especially if they had a negative experience. In order to minimise this effect another interviewer (LW), with no previous involvement with the Magpie Trial or the QUOTE Study was enlisted. This interviewer was also a midwife and aware of the aims and procedures of the Magpie Trial and its follow up study. Comprehensive information was also supplied about the QUOTE Study. Periodically we both met, read over each other's interview transcripts and discussed similarities and differences. We found no variations

in the answers given by the women that could be attributed to giving more desirable responses to me than to any non-involved colleague.

Although the sample of forty women interviewed cannot be considered completely typical of the study population, I have no reason to suppose that these findings would not be generalisable to other women recruited to the Magpie Trial as well as those participating in other perinatal trials, at least in the UK. The interviews proved to be an effective method to explore experiences of joining Magpie, and data from the postal questionnaires verified much of what the women described in the interviews.

Despite the above limitations, this study has provided insights into the women's views and experiences of joining a perinatal trial. The postal questionnaires proved an effective means of gaining understanding of trial experience, the interviews provided a greater understanding.

9.5 Implications for research

This study has contributed to a greater understanding of the views and experiences of those recruited to perinatal trials. In addition a contribution has been made to the growing body of knowledge pertaining to the conduct of randomised controlled trials. As with all research, as many questions are raised by the work as answered. While this study hopefully moves the subject forward in a number of ways, further topics remain to be examined. As a result I want to make the following suggestions for the focus, design and conduct of future studies exploring women's experiences of perinatal randomised controlled trials:

- Further assessment of the level at which trial participants feel able to make an informed decision to participate, to what extent they felt the informed consent process is acceptable; and how various factors influence their experiences of the consent process;

- Examination of the impact of antenatal provision of information regarding potential research; whether prior exposure helps with obtaining fully informed consent; and what effect it has on understanding of the study, satisfaction with participation and overall recruitment rates;

- Further examination of women's attitudes regarding the concepts: altruism, unwitting coercion, and therapeutic misconception, including the previously neglected concept of clinical equipoise;

- Research examining how clinicians communicate information about clinical trials to potential participants; what degree of uncertainty exists among individual clinicians; and whether an individual clinician's preference should be revealed to potential participants;

- Further assessment of the direct involvement and impact of partners and the family in the informed consent process and on decision-making;

- Investigation of the double standards of consent and information provision for trial participation compared with that provided in normal clinical practice;

- Further consideration of the views of those declining participation. Despite being extremely valuable for the planning of future trials there has been relatively little direct research on non-participants and why they choose not to participate in a trial;

- Further research assessing the preferences of research participants about receiving study results; and their reactions to such disclosure is required. Much work needs to be done in this area to explore the most appropriate means of returning results, and about the cost and time required to do so. Further research is needed to develop and test

planned debriefing of trial participants about their allocated trial treatment and researchers attitudes towards communicating this information;

- Further research to ascertain the extent of which the findings of this study are applicable to women participating in different types of perinatal research trials. Research nested in ongoing trials, taking a longitudinal approach, would allow demonstration of how preferences and opinions change over the course of pregnancy. One aspect of this challenge may relate to the views of recruiting clinicians themselves and their understandings of the trial design.

9.6 Implications for practice

The study findings demonstrate some of the difficulties women experience when considering joining a trial in the perinatal period. The general implication for practice is that procedures are needed that can improve the design and conduct of randomised trials and therefore ultimately enhance the experience for future women. Recommendations include:

- The need to educate the general public about the necessity for clinical trials and about the manner in which randomised trials are conducted;

- The importance of involving users in any future trials at all stages, and most significantly during the planning stages, in order to identify trial conduct considered to be most suitable;

- Informed consent should be tailored, recognising individual differences in the desire for information. For instance the time individuals need to make consent decisions varies, as do their desires to consult with family before agreeing to a study. The opportunity should be made available for participants to ask questions and the need for repetition and elaboration acknowledged. When explaining the trial clinicians should use simple language. The consent process should include particular attention to the distinctions between procedures performed

as part of the trial and procedures performed as part of routine clinical practice;

- The fact that the results will be offered and provided in the future should be built into the informed consent process so that participants are aware of the plan and have the opportunity to decline receipt. Returning the results should be done in a careful and well-planned manner that provides comprehensive support; with an invitation to contact the researcher for a verbal discussion if the participant wishes. Researchers should budget for the costs of returning results including maintaining contact with research participants. Methods to disseminate the results should be included in research protocols;

- Offering unblinding of treatment arms on completion of the trial should be made available. Similar to the provision of results this needs to be well planned and done carefully. Procedures need to provide full support to participants, with available contact with the researchers for verbal discussion if they wish.

- The Magpie Trial follow up study is an example to trialists of how exploring participants' views can be done relatively easily. The three questions added to the routine follow up survey allowed information to be obtained from a large number of women throughout the UK about their trial experience. The cost (both financial and time) of adding the three questions and analysing the data was relatively cheap when compared with that of the interviews. Future trials (and their follow up studies) should consider including questions about trial experience to any routine trial surveys.

I believe these practical suggestions may help improve the experience of women participating in future perinatal trials, which the ultimate goal is to improve outcomes in pregnancy and childbirth.

9.7 Provision of the results of the follow up and QUOTE Study

Soon after completion of the analysis of the Magpie follow up study the women recruited in the UK were sent a summary of the results (Appendix 19). The one page summary began with thanking the women and acknowledging the contribution they had made to the trial; it included an introductory paragraph about the Magpie Trial and its results (aimed as a reminder), a description of the follow up study and a summary of the findings with regard to both women's and children's outcomes. The summary informed the women that the follow up study did not find clear evidence that giving magnesium sulphate to women with pre-eclampsia influenced their health or their children's health two years later. The citations of the medical publications were included.

In keeping with this ethos a summary of the results of QUOTE will be sent to the forty women interviewed. The summary will include an introductory letter thanking the women for their initial participation in the Magpie Trial and its follow up (Appendix 20). The one-page summary describes the QUOTE findings (Appendix 21) and will be sent to coincide with the publication of the main results.

9.8 Closing remarks

It is undisputed that clinical research is important for the continued development of health care and the wellbeing of society, and the Magpie Trial produced compelling evidence about the optimal management of pre-eclampsia, both in the short and longer-term. There remains, however, a vital need to perform research into many of the other elements of care given during pregnancy and childbirth. With this need comes the ethical responsibility of researchers to ensure trials are performed in the most scientifically robust and acceptable way. To assess the understanding and experience of those involved in trial participation is a crucial way of facilitating this. The QUOTE Study advances understanding of the experiences of those participating in a randomised controlled trial. As more data of the type reported here accumulate, clinicians and researchers will have the option to modify research strategies to reflect actual participants' concerns and needs.

The Magpie Trial was a remarkable achievement and has undoubtedly saved and improved women's and babies lives throughout the world. It is vital high-quality research continues and it is important we find out more about the experiences of those we (society) are indebted to. I have had the very fortunate experience of being involved in all stages of the Magpie Trial: the main trial, its follow up study, and finally exploration of the women's experiences of participating, which forms the focus of this thesis and I hope contributes to this body of knowledge.

Articles

Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial

*The Magpie Trial Collaborative Group**

Summary

Background Anticonvulsants are used for pre-eclampsia in the belief they prevent eclamptic convulsions, and so improve outcome. Evidence supported magnesium sulphate as the drug to evaluate.

Methods Eligible women (n=10 141) had not given birth or were 24 h or less postpartum; blood pressure of 140/90 mm Hg or more, and proteinuria of 1+ (30 mg/dL) or more; and there was clinical uncertainty about magnesium sulphate. Women were randomised in 33 countries to either magnesium sulphate (n=5071) or placebo (n=5070). Primary outcomes were eclampsia and, for women randomised before delivery, death of the baby. Follow up was until discharge from hospital after delivery. Analyses were by intention to treat.

Findings Follow-up data were available for 10 110 (99·7%) women, 9992 (99%) of whom received the allocated treatment. 1201 of 4999 (24%) women given magnesium sulphate reported side-effects versus 228 of 4993 (5%) given placebo. Women allocated magnesium sulphate had a 58% lower risk of eclampsia (95% CI 40–71) than those allocated placebo (40, 0·8%, vs 96, 1·9%; 11 fewer women with eclampsia per 1000 women). Maternal mortality was also lower among women allocated magnesium sulphate (relative risk 0·55, 0·26–1·14). For women randomised before delivery, there was no clear difference in the risk of the baby dying (576, 12·7%, vs 558, 12·4%; relative risk 1·02, 99% CI 0·92–1·14). The only notable difference in maternal or neonatal morbidity was for placental abruption (relative risk 0·67, 99% CI 0·45–0·89).

Interpretation Magnesium sulphate halves the risk of eclampsia, and probably reduces the risk of maternal death. There do not appear to be substantive harmful effects to mother or baby in the short term.

Lancet 2002; **359**: 1877–90
See *Commentary page 1872*

Introduction

Pre-eclampsia, a multisystem disorder of pregnancy usually associated with raised blood pressure and proteinuria, complicates 2–8% of pregnancies.[1] Although outcome is often good, pre-eclampsia is a major cause of morbidity and mortality for the woman and her child.[2] Eclampsia is defined as the occurrence of one or more convulsions superimposed on pre-eclampsia. In developed countries eclampsia is rare, affecting around one in 2000 deliveries,[3] while in developing countries estimates vary from one in 100 to one in 1700.[4,5] Worldwide an estimated 600 000 women die each year of pregnancy-related causes,[4] with 99% of these deaths occurring in developing countries. Pre-eclampsia and eclampsia probably account for more than 50 000 maternal deaths a year.[3] In places where maternal mortality is high, most of these deaths are associated with eclampsia. Where maternal mortality is lower, a higher proportion will be due to pre-eclampsia. For example, in the UK pre-eclampsia and eclampsia together account for 15% of direct maternal deaths, and two-thirds were related to pre-eclampsia.[2]

For decades anticonvulsant drugs have been given to women with pre-eclampsia, in the belief that they reduce the risk of seizure, and so improve outcome.[1] However, there has been little reliable evidence to support that belief. In 1998, a systematic review[6] of anticonvulsants for women with pre-eclampsia identified four trials (total 1249 women) comparing an anticonvulsant with no anticonvulsant or placebo. This review concluded that magnesium sulphate was the most promising choice for pre-eclampsia, and the priority for further evaluation. Additionally, magnesium sulphate is now the drug of choice for women with eclampsia, with strong evidence that it is better than either diazepam,[7,8] phenytoin,[11] or lytic cocktail.[12]

The use of magnesium sulphate for pre-eclampsia is increasing,[13] although a range of other anticonvulsant drugs continue to be used, including diazepam and other benzodiazepines, phenytoin, barbiturates, and lytic cocktail. There is also substantial variation in the severity of pre-eclampsia for which a prophylactic anticonvulsant is used. In the USA, for example, magnesium sulphate is given to an estimated 5% of pregnant women before delivery.[14] By contrast, a quarter of UK obstetricians never use any prophylactic anticonvulsants,[15] and those who do often restrict their use to women with severe pre-eclampsia, which is around 1% of deliveries.

The initial question about magnesium sulphate, as a prophylactic anticonvulsant for women with pre-eclampsia, is whether it reduces the risk of eclampsia. Even if it does, reliable information is required before magnesium sulphate can be safely recommended for clinical practice; in particular about the size of any risk reduction, effects on other important outcomes for the woman and child, and disease severity at which benefits outweigh the risks. The Magpie Trial (MAGnesium sulphate for Prevention of Eclampsia) was a large

*Members listed at end of paper

Correspondence to: Dr Lelia Duley

Resource Centre for Randomised Trials, Institute of Health Sciences, Headington, Oxford OX3 7LF, UK
(e-mail: lelia.duley@ndm.ox.ac.uk)

international trial designed to evaluate the effects of magnesium sulphate on women and their babies. The aim was to find out if, overall, women with pre-eclampsia or their children, or both, do better if they are given magnesium sulphate rather than placebo, regardless of whether treatment is started before or after delivery and irrespective of any previous anticonvulsant therapy.

Methods

Trial organisation

Overall coordination of the trial was from the Resource Centre for Randomised Trials at the Institute of Health Sciences in Oxford, UK. Spanish speaking centres in Latin America were coordinated from the Centro Rosarino de Estudios Perinatales in Rosario, Argentina, and from the Instituto Argentino de Medicina Basada en las Evidencias in Buenos Aires, Argentina. Centres in South Africa were coordinated from the MRC Pregnancy Hypertension Unit in Durban. Throughout recruitment, a 24-h on-call service was provided by the Coordinating Centre in Oxford. Trial procedures were piloted at Kalafong Hospital, Pretoria, in South Africa (February to July, 1998). Recruitment to the pilot trial took place between Feb 23, and July 14, 1998 (n=101), and to the main trial between July 15, 1998, and Nov 29, 2001.

All hospitals were required to secure appropriate local ethics or research committee approval before recruitment could begin. In the UK, the trial was approved by the Northwest Multicentre Research Ethics Committee. It was also approved by the WHO Scientific and Ethical Review Group, Geneva, Switzerland.

Participants

Women were eligible for trial entry if they had pre-eclampsia and there was uncertainty about whether to use magnesium sulphate. We included women irrespective of whether they had had an anticonvulsant at a referring hospital, or whether the pregnancy was singleton or multiple. Most women were recruited whilst on the labour ward. Although the decision to offer participation was usually made by the obstetrician, women could be enrolled by either an obstetrician or a midwife. Eligibility criteria were: the woman had not given birth, or was 24 h or less postpartum; blood pressure was 90 mm Hg diastolic or 140 mm Hg systolic or more on at least two occasions; proteinuria was 1+ or more; and there was clinical uncertainty about whether magnesium sulphate would be beneficial. Women were excluded if they had hypersensitivity to magnesium, hepatic coma with a risk of renal failure, or myasthaenia gravis. Women with oliguria (urine output <25 mL/h) were eligible, but the volume of trial treatment was halved for each dose. All women provided written or oral informed consent.

It was anticipated that uncertainty about the use of magnesium sulphate would be affected by the presence of signs or symptoms of imminent eclampsia, such as hyper-reflexia, frontal headache, blurred vision, and epigastric tenderness. If the woman's initial blood pressure did not require immediate treatment, it was recommended that the two measurements should be 30 min apart, but up to 1 h between measurements was allowed. If the initial blood pressure was high enough to require consideration of immediate antihypertensive treatment, the second measurement was taken within 30 min. For assessment of proteinuria, a midstream sample was requested whenever possible. Because eligibility was highly dependent on the attending clinicians' beliefs about magnesium sulphate it was not possible to keep an accurate record of those eligible but not recruited.

Randomisation

Hospitals with reliable access to telephones used a central telephone randomisation service at the Clinical Trial Service Unit, in Oxford. Baseline details were collected during a 2–3 min call, and recorded on the central computer. Treatment allocation used a minimisation algorithm, balancing for severity of pre-eclampsia, gestation at randomisation, whether delivered, whether given anticonvulsant drugs before trial entry, whether a multiple pregnancy, and country. The allocated pack number was then given and recorded on the trial entry form. Hospitals without reliable access to telephones used a local pack system. Baseline information was collected on the trial entry form and the next consecutively numbered pack taken from the box of eight packs (with an allocation sequence based on a block size of eight, also generated by the Clinical Trial Service Unit). The pack number was recorded on the form, which was then faxed to the Coordinating Centre in Oxford. The woman was in the trial once this number had been recorded, regardless of whether the pack was opened or the allocated treatment started.

The boxes of eight treatment packs had a large lift-up flap on one side, to display all the pack numbers when using the telephone randomisation service. The other side had a small horizontal flap at the bottom, allowing only one box to be removed at a time for those using the local box system. Treatment packs were prepared and packed by an independent clinical trial supplies company (DHP Clinical Supplies, Abergavenny, Wales, UK). Each batch of active and placebo packs was tested by an independent biochemist before distribution.

Interventions

Women were randomly allocated to receive either magnesium sulphate or placebo. Each woman was assigned a uniquely numbered treatment pack, containing nine 10 mL ampoules labelled "Magpie Trial Treatment". Each 10 mL "active" ampoule contained 5 g magnesium sulphate heptahydrate ($MgSO_4.7H_2O$) 50% solution, which is approximately 2 mmoL magnesium/mL. Each placebo ampoule contained 10 mL normal saline. The magnesium sulphate and placebo ampoules were identical, and the solutions looked the same. Each pack also contained 10 mL calcium gluconate, for use in the event of toxicity, and an eclampsia rescue pack (see below) for use in the event of eclampsia. Treatment packs were provided to collaborating hospitals in boxes of eight packs. Standard treatment was a loading dose followed by 24-h maintenance therapy, with clinicians at each hospital able to choose whether to use the intravenous (iv) or the intramuscular (im) routes for the maintenance regimen. These two magnesium sulphate regimens were chosen because they are both widely used internationally, and have been evaluated in trials for treatment of women with pre-eclampsia[4] and eclampsia.[10–12]

The loading dose was 8 mL trial treatment (4 g magnesium sulphate, or placebo). This solution was diluted with normal saline according to whatever was the usual local practice, and given iv over 10–15 min. For the iv maintenance regimen,[13] this preliminary dose was followed by an infusion over 24 h of 2 mL/h trial treatment (1 g/h magnesium sulphate, or placebo), again diluted with normal saline, according to usual local practice. For the im maintenance regimen[14] this initial iv dose of 8 mL trial treatment was combined with 20 mL trial treatment by im injection, given as 10 mL trial treatment (5 g magnesium sulphate or placebo) into each

buttock. This dose was followed by 10 mL trial treatment (5 g magnesium sulphate, or placebo) every 4 h, for 24 h.

Two hospitals in Bangladesh used a loading dose of 20 mL trial treatment (10 g magnesium sulphate, or placebo), given as 8 mL trial treatment *iv* over 10–15 min followed by 5 mL trial treatment (2·5 g magnesium sulphate, or placebo) im into each buttock, and then 5 mL trial treatment (2·5 g magnesium sulphate, or placebo) every 4 h for 24 h.

If the woman had recently received a loading dose of magnesium sulphate at a referring hospital, she could be randomised and the trial treatment loading dose omitted. The *iv* regimen required six ampoules of trial treatment (58 mL), and the im regimen eight ampoules (78 mL). The extra ampoules in each pack could be used to continue trial treatment beyond 24 h, if this was considered necessary by the clinicians. An additional pack of nine ampoules could be allocated to the women if treatment was to continue for longer than was possible with one treatment pack, or if treatment was to be restarted some time later. In this situation, the central 24-h randomisation service (see above) or the Coordinating Centre in Oxford was contacted and an additional treatment pack allocated, which contained the same treatment as the first pack. If it was not possible to make this contact, the clinicians had to decide whether or not to use ward stock magnesium sulphate. All other aspects of care were at the discretion of the clinicians.

Magnesium sulphate is excreted by the kidneys and is a smooth muscle relaxant. Reduction or loss of tendon reflexes precedes respiratory depression, so reflexes were to be carefully monitored and magnesium sulphate administration adjusted as appropriate to prevent toxicity. Before starting Magpie Trial treatment, the clinician checked that knee or other tendon reflexes were present, the respiratory rate was normal (>16 respirations/min), and urine output was 100 mL or more during the past 4 h, or greater than 25 mL/h. Clinical monitoring continued throughout trial treatment, with reflexes and respiration to be checked at least every 30 min (or according to usual practice) and urine output measured hourly for the duration of treatment. The volume of trial treatment was reduced by half if tendon reflexes were slow, respiratory rate reduced but the woman well oxygenated, or urine output was less than 100 mL in 4 h. Blood monitoring of magnesium concentrations was not required.

Unblinding was available either by phoning the telephone randomisation service in Oxford or by using the 24-h emergency bleep, usually held by either the Clinical Coordinator or the Trial Manager. To preserve the blinding, clinicians were asked not to measure serum magnesium concentrations, unless clinically necessary, and to report if any measurements were taken.

If the woman had an eclamptic seizure, trial treatment was to be stopped and it was recommended that magnesium sulphate be used. Rather than unblind the allocation before initiation of treatment, which might have led to unacceptable delays, an eclampsia rescue pack was provided in each treatment pack, with two red labelled ampoules. One contained 5 g magnesium sulphate and the other 10 mL of either 50% magnesium sulphate (5 g) or placebo, whichever was the opposite of the trial allocation. For management of the acute fit, 4 mL from each ampoule were given *iv* over 5–10 min; 4 g magnesium sulphate for those originally allocated placebo and 2 g for those originally allocated magnesium sulphate. Magnesium sulphate maintenance therapy was then to be continued according to the normal clinical practice in that hospital. If the im Magpie Trial regimen had been used, the first unblinded im dose for eclampsia was given when the next trial treatment dose would have been due, to avoid overdose.

Outcomes

Primary outcomes were eclampsia and, for women randomised before delivery, death of the baby before discharge from hospital (including stillbirths). Maternal death was not specified as a primary outcome, because the study was not expected to have sufficient power to estimate reliably any effects on maternal mortality. Cause of death for the babies was classified using the system suggested by Wigglesworth.[17] Because most babies were from countries where normal birthweight tends to be lower than in the UK, where this classification system was devised, we used a birthweight of 2 kg or less (rather than ≤2·5 kg) for prematurity. Follow-up for women and children was until discharge from hospital after delivery. Long-term follow-up of a proportion of the women and children is also under way at selected centres.

Secondary outcomes were measures of serious maternal morbidity (respiratory depression, respiratory arrest, pneumonia, cardiac arrest, coagulopathy, renal failure, liver failure, pulmonary oedema, and cerebral haemorrhage), toxicity (need for calcium gluconate, stopped or reduced treatment due to toxicity, stopped or reduced treatment due to side-effects), and other side-effects of magnesium sulphate (nausea or vomiting, flushing of the skin, drowsiness, confusion, muscle weakness, abscess). A composite outcome of these nine measures of serious morbidity was also prespecified as a main outcome. Serious unexpected events thought possibly to be related to the trial treatment were reported immediately to the Coordinating Centre in Oxford.

For women randomised before delivery, additional secondary outcomes were complications of labour and delivery (induction and length of labour, caesarean section, retained placenta, blood loss, transfusion, and gestation at delivery), and neonatal morbidity (Apgar <7 at 5 min, intubation at place of delivery, ventilation, abnormal cerebral ultrasound, convulsions, and admission to special care baby unit).

Other outcomes included measures of the use of maternal health-service resources (number of days in hospital, admission to an intensive care unit or a high

Definition of severe pre-eclampsia

All women

Diastolic blood pressure ≥110 mm Hg on two occasions, or systolic blood pressure ≥170 mm Hg on two occasions and proteinuria ≥3+

or

Diastolic blood pressure ≥100 mm Hg on two occasions, or systolic blood pressure ≥150 mm Hg on two occasions and proteinuria ≥2+ and at least two signs or symptoms of imminent eclampsia

Or, for women who had an antihypertensive in the 48 h before randomisation

In 48 h before trial entry, highest diastolic blood pressure ≥110 mm Hg, or highest systolic blood pressure ≥170 mm Hg and proteinuria ≥3+ at trial entry

or

In 48 h before trial entry, highest diastolic blood pressure ≥100 mm Hg, or highest systolic blood pressure ≥150 mm Hg and proteinuria ≥2+ and at least two signs or symptoms of imminent eclampsia

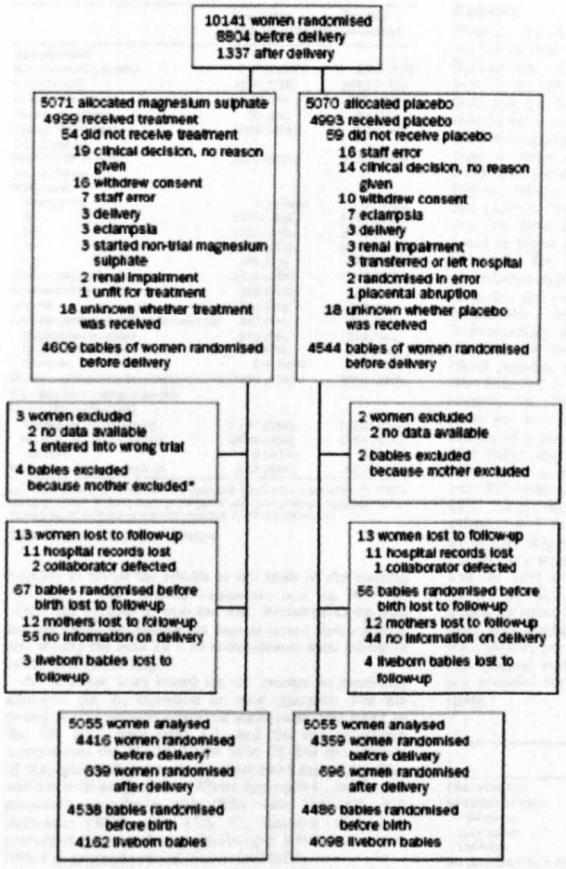


Figure 1: Trial profile
*Includes one pair of twins. †Includes one phantom pregnancy.

dependency unit, ventilation, and dialysis) and of neonatal health-service resources (days in special care baby unit and ventilation). An economic evaluation of the use of magnesium sulphate for women with pre-eclampsia is in progress.

Subgroup and sensitivity analyses

Women were classified, a priori, into subgroups based on their characteristics at trial entry: severity of pre-eclampsia, imminent eclampsia, gestational age, whether they had an anticonvulsant in the previous 48 h, and whether they had already given birth. The protocol defined severe pre-eclampsia at randomisation according to the criteria in the panel. Imminent eclampsia was taken as two or more signs or symptoms of imminent eclampsia regardless of hypertension and proteinuria.

Outcome was also compared on the basis of the country's perinatal mortality, as reported by WHO.[18] Although these subgroups were not specified until just before the final analysis, a similar strategy had been used successfully in an earlier perinatal trial.[10] Low perinatal mortality was taken as less than 20 deaths per 1000 births, moderate as 20–40 per 1000 births, and high as more than 40 per 1000 births. Countries with low perinatal mortality were Albania, Australia, Canada, Cuba, Denmark, Israel, Italy, Singapore, The Netherlands, UK, and USA. Countries with moderate perinatal mortality were Argentina, Colombia, Jordan, Malaysia, Mexico, Sri Lanka, Thailand, United Arab Emirates, Venezuela, and Zimbabwe. Countries with high perinatal mortality were Bangladesh, Brazil, Egypt, Ghana, India, Malawi, Nigeria, Pakistan, Sierra Leone, South Africa, Uganda, and Yemen.

Statistical analysis

We initially estimated that the risk of convulsions for women allocated placebo might be around 1%, and that to have 90% power to show a 50% decrease in this risk would require 14 000 women (α=0·05). In February, 2000, the sample size estimate was revisited, because the overall risk of eclampsia among trial participants was 1·2%. After consultation with the chair of the data monitoring committee, target recruitment was revised to between 10 800 and 12 750 women. We expected that most women (90%) would be randomised before delivery. If total mortality for their babies was 12%, as in previous trials,[1] our enrolment target would give a power of 90% to detect a 15% proportional reduction to 10·2% (α=0·05). If total mortality for the babies was reduced from 10% to 8·5% (15% reduction), the power would be 80% (α=0·05).

Data were monitored, in strict confidence, by an independent data monitoring committee. Meetings of the committee were arranged as considered appropriate by the chair. The committee's terms of reference were that they should inform the chair of the steering committee if, in their view: there was proof beyond reasonable doubt that treatment with magnesium sulphate was clearly indicated or contraindicated, and there was a reasonable expectation that this new evidence would materially affect patients' management; or if it was evident that no clear outcome would be obtained. Proof beyond reasonable doubt required a difference of at least 3 SE in at least one of the primary outcomes, which corresponds to a p value of about 0·003.

At their fifth meeting on Nov 27, 2001, after review of data for 8483 women with follow-up to discharge from hospital after delivery, the data monitoring committee

	Magnesium sulphate (n=5068)*	Placebo (n=5068)†
Characteristic		
Age (mean, SD) (years)	27·1 (6·7)	27·2 (6·7)
Primiparous‡	2604 (52%)	2591 (51%)
Multiple pregnancy	217 (4%)	203 (4%)
History of epilepsy	56 (1%)	56 (1%)
Systolic BP at entry >170 mm Hg	801 (16%)	806 (16%)
Diastolic BP at entry >110 mm Hg	1119 (22%)	1146 (23%)
Proteinuria		
Trace/none	2 (0·04%)	5 (0·1%)
1+	1571 (31%)	1568 (31%)
2+	1704 (34%)	1721 (34%)
3+	1310 (26%)	1270 (25%)
4+	481 (9%)	504 (10%)
Severe pre-eclampsia	1303 (26%)	1349 (27%)
Imminent eclampsia§	816 (16%)	833 (16%)
Oliguria	131 (3%)	129 (3%)
Previous treatment with anticonvulsant	440 (9%)	435 (9%)
Magnesium sulphate	242 (5%)	241 (5%)
Other anticonvulsant	196 (4%)	192 (4%)
Unknown	2 (0·04%)	2 (0·04%)
Previous treatment with antihypertensive	2508 (49%)	2502 (49%)
If treated with antihypertensive, highest BP before entry		
Systolic BP >170 mm Hg	1149 (23%)	1172 (23%)
Diastolic BP >110 mm Hg	1540 (30%)	1554 (31%)
Unknown	8 (0·2%)	4 (0·1%)
Postpartum at randomisation	640 (13%)	697 (14%)

BP=blood pressure. *Three women excluded. †Two women excluded. ‡n=5065 for both groups. §Two or more of frontal or severe headaches, epigastric pain, blurred vision, or hyper-reflexia (irrespective of BP or proteinuria).

Table 1: Baseline characteristics

decided to reveal the results to the chair of the steering committee. The steering committee met on Nov 29, 2001, and decided to stop the trial. Recruitment through the telephone randomisation service closed that evening, and during the next 24 h all collaborators were informed of the decision to stop.

All analyses were based on the groups as randomly allocated (ie, an intention to treat analysis). For the principal comparisons statistical significance was taken as the 5% level with 95% CI, and for the secondary comparisons the 1% level with 99% CI. For the analysis of multiple births, outcome was assessed for total babies and for total pregnancies. Where appropriate, results are presented as relative risk (RR) with 95% CI, risk difference (RD) with 95% CI, number of events prevented (compared with placebo) per 1000 women with 95% CI, or number needed to treat (NNT).

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Magnesium sulphate (n=4427)*	Placebo (n=4373)
Characteristic		
Gestation at entry		
<34 weeks	1211 (27%)	1213 (28%)
≥34 weeks	3215 (73%)	3158 (72%)
Severe pre-eclampsia at entry	1150 (26%)	1182 (27%)
Multiple pregnancy†	173 (4%)	167 (4%)
Fetal heartbeat not heard at entry‡	143 (3%)	151 (3%)

Data are number (%). *Excludes one woman with a phantom pregnancy. †Magnesium sulphate: 168 twins, five triplets; placebo: 165 twins, two triplets. ‡n=4605 magnesium sulphate and n=4542 placebo (includes two babies where mother randomised between delivery of twin one and two).

Table 2: Characteristics at trial entry for women randomised before delivery

Results

Overall, 10 141 women were randomised at 175 secondary and tertiary level hospitals in 33 countries. Recruitment of 101 women in the pilot occurred from Feb 23, to July 14, 1998, and of the remaining women from July 15, 1998, to Nov 29, 2001. Altogether, 2037 women were recruited through the telephone service and 8104 through the local pack system. 4762 (47%) women were recruited in Africa, 2735 (27%) in the Americas, 1583 (15%) in the Asia-Pacific region, and 1061 (10%) in Europe. Of these, five women have been excluded from this analysis (three from the magnesium sulphate group and two from placebo). The reasons for exclusion are listed in figure 1. A further six treatment packs are not accounted for. 15 women randomised in two different pregnancies appear twice. 18 women who did not fully meet the entry criteria are included; five were allocated magnesium sulphate (two had proteinuria <1+ [<30 mg/dL]), three were >24 h after delivery) and 13 placebo (five had proteinuria <1+, three did not meet blood pressure criteria, five were >24 h after delivery). Also included is a woman with a phantom pregnancy. 17 women with a history of a possible convulsion before trial entry are also included. For eight of these women the history of a possible convulsion was only obtained after trial entry; the other nine were randomised in error. Information at trial entry is available for 10 136 women, and follow-up data are available for 10110 (99·7%). 9153 babies were born to women randomised before delivery, and data are available for 9024 (98·6%). Of these, 127 may have died in utero before randomisation, because the fetal heart beat was not heard at trial entry and the baby was a macerated stillbirth born less than 24 h later. For secondary outcomes, missing data for individual items is only reported if they constituted 1% of total data available. For most outcomes, less than ten were missing per group, with the exception of steroid use and manual removal of retained placenta, which were not available for the 101 women recruited to the pilot study.

	Magnesium sulphate (n=640)	Placebo (n=697)*
Characteristic		
Gestation at birth		
<34 weeks	112 (18%)	135 (19%)
≥34 weeks	519 (81%)	556 (80%)
Unknown	9 (1%)	6 (1%)
Randomised >24 h after delivery†	3 (0·5%)	5 (0·7%)
Severe pre-eclampsia at entry	152 (24%)	166 (24%)
Multiple pregnancy	44 (7%)	36 (5%)
Birthweight (g)‡		
<1500	94 (14%)	107 (15%)
<2500	340 (49%)	354 (48%)
Total baby deaths‡	58 (8%)	85 (12%)
Perinatal death‡	48 (7%)	78 (11%)
Stillbirth	32	56
Early neonatal death	16	22
Late neonatal deaths‡	8	3
Post neonatal deaths‡	2	4
Cause of death‡		
Congenital malformation	1	4
Asphyxia	23	29
Macerated stillbirth	14	33
Prematurity	16	17
Other	4	2

*Includes two women randomised between delivery of twin one and twin two. †n=639 magnesium sulphate, n=696 placebo. ‡n=687 magnesium sulphate, 40 twins and four triplets; n=731 placebo, 33 twins and one triplet, plus twin one for two women randomised between delivery of twin one and twin two.

Table 3: Characteristics at trial entry for women randomised after delivery

	Magnesium sulphate (n=5055)	Placebo (n=5055)
Received allocated treatment*	4999 (99%)	4993 (99%)
Unknown	2 (0·04%)	3 (0·06%)
Received allocated treatment plus		
No other drug	4736 (94%)	4742 (94%)
Non-trial magnesium sulphate	126 (2%)	104 (2%)
Non-trial magnesium sulphate and diazepam	2 (0·04%)	9 (0·2%)
Diazepam	104 (2%)	114 (2%)
Phenytoin	7 (0·1%)	4 (0·08%)
Barbiturates	14 (0·3%)	13 (0·3%)
Other†	10 (0·2%)	9 (0·2%)
Did not receive allocated treatment	54 (1%)	59 (1%)
No other anticonvulsant	46 (0·9%)	48 (0·9%)
Non-trial magnesium sulphate alone	6 (0·1%)	9 (0·2%)
Other‡	2 (0·04%)	2 (0·04%)
Duration of treatment (median, IQR) (h)§	24·2 (24·0–25·6)	24·2 (24·0–25·6)
Additional treatment pack used¶	31 (0·6%)	27 (0·5%)
<2 h from end of first pack to start of second	10 (0·2%)	11 (0·2%)
Serum magnesium measured	39 (0·8%)	41 (0·8%)
Volume of treatment		
Intravenous regimen, given 58 mL‖	1688 (62%)	1679 (62%)
Intramuscular regimen, given 78 mL‖	1427 (66%)	1532 (70%)
Treatment stopped early		
Total	785 (16%)	631 (13%)
Woman's request or side-effects	317	118
Oliguria or renal failure	114	148
Woman stable	72	68
Staff error**	99	56
Absent tendon reflexes	47	50
Decided to use magnesium sulphate	29	28
No bed space or equipment failure	28	35
Respiratory depression or arrest	26	14
Eclampsia	16	54
Hypotension	16	7
For caesarean section	15	9
Severe medical problem	7	10
Transferred or left hospital	7	9
Eclampsia before trial entry, randomised in error	1	2
Woman died	2	0
Other	10	7

*Includes six women in each group given wrong pack with wrong allocated treatment. †Includes ipsc oxolcain, carbamazepine, chlorpromazine, nitrazepam; seven women (five magnesium sulphate, two placebo) not known which anticonvulsant used, and five (two magnesium sulphate and three placebo) had two additional anticonvulsants. ‡Magnesium sulphate plus diazepam, diazepam alone, or unknown. §Calculated either up to time infusion stopped, or 4 h after last intramuscular injection; includes additional treatment if started within 2 h of finishing first pack. ¶For 16 women additional one pack was not allocated correctly; of these, seven allocated magnesium sulphate had placebo in additional pack, one allocated placebo had magnesium sulphate in additional pack. ‖Includes additional treatment if started within 2 h of finishing the first pack; for intravenous route n=2719 magnesium sulphate, n=2720 placebo; for intramuscular route n=2193 magnesium sulphate, n=2184 placebo (excludes two centres in Bangladesh, which used a different regimen). **20 women allocated magnesium sulphate and 17 placebo from one centre where protocol initially misunderstood.

Table 4: Compliance with allocated treatment

The groups were well balanced at trial entry (table1). Just over half the women were in their first pregnancy, 4% had multiple pregnancies, 26% had severe pre-eclampsia, and 16% imminent eclampsia, 9% had received an anticonvulsant before trial entry, and 13% were recruited postpartum. Only 3% (138 of 5068 magnesium sulphate vs 155 of 5068 placebo) of women had blood pressure of 140/90 mm Hg and 1+ protein, the minimum criteria. The proportion of women with severe pre-eclampsia at trial entry in each country ranged from none of 43 in the USA and three of 261 (1%) in Cuba to 58 of 108 (54%) in Egypt and 21 of 37 (57%) in Sierra Leone. This variation probably reflects the local clinicians' prior belief about the value of magnesium sulphate; so, for example, in the USA and Cuba most women with severe pre-eclampsia were given magnesium sulphate rather than recruited to the trial. 26% (2524 of 9690) of women with singleton pregnancies had severe pre-eclampsia, as did 28% (118 of 420) of those with multiple pregnancies. For women randomised before delivery, a quarter were less than 34 weeks at trial entry (table 2). Of those randomised after delivery, 18% were less than 34 weeks at delivery (table 3). The small imbalance between the groups for women randomised before (4428 vs 4371) or after delivery (640 vs 697) appears to be due to the chance accumulation of slight imbalances in a small number of centres using the local pack system (data not shown).

	Magnesium sulphate (n=4999)	Placebo (n=4993)
Side-effects	1201 (24%)	228 (5%)
Flushing	987	98
Nausea or vomiting, or both	160	18
Muscle weakness	72	6
Absent or reduced tendon reflexes	59*	60
Respiratory depression or other problems	51*	26
Thirst	37	11
Headache	36	17
Hypotension or palpitations or tachycardia	36	9
Dizziness	37	10
Drowsiness or confusion	20	9
Itching or tingling	15	1
Other	20	9
Problems at injection site—intravenous regimen†	125 (5%)	41 (2%)
Pain or burning	95 (3%)	15 (0·6%)
Drip tissued	22 (0·8%)	17 (0·6%)
Inflammation or phlebitis	7 (0·3%)	8 (0·3%)
Bruising	1 (0·04%)	1 (0·04%)
Problems at injection site—intramuscular regimen‡	271 (12%)	181 (8%)
Pain or burning	244 (11%)	170 (8%)
Inflammation or phlebitis	17 (0·7%)	4 (0·2%)
Bruising or bleeding	9 (0·4%)	0
Abscess	1 (0·04%)	1 (0·04%)

Some women had more than one side-effect. *Four women had respiratory depression and absent tendon reflexes. †n=2719 magnesium sulphate, n=2720 placebo. ‡n=2280 magnesium sulphate, n=2273 placebo.

Table 5: Side-effects and problems at injection site, for women who received trial treatment

	Magnesium sulphate (n=5055)	Placebo (n=5055)	Relative risk (95% CI)
Eclampsia	40 (0·8%)	96 (1·9%)	0·42 (0·29 to 0·60)*
Unknown	4 (0·08%)	3 (0·06%)	
Number of fits			
1	27	69	
2	10	24	
3	2	7	
>4	1	1	
Unknown	0	1	
Maternal death	11 (0·2%)	20 (0·4%)	0·55 (0·26 to 1·14)†
Unknown	2 (0·04%)	2 (0·04%)	
Main cause of death			
Cardiac arrest or failure	4	6	
Stroke	3	2	
Eclampsia or pre-eclampsia	1	2	
Anaemia or postpartum haemorrhage	1	1	
Anaesthetic death	1	0	
Respiratory failure or pneumonia	1	1	
Renal failure	0	3	
Pulmonary embolism	0	3	
Infection	0	2	

Risk difference (95% CI) is *–1·1 (–1·6 to –0·7), †–0·2 (–0·4 to 0·04).

Table 6: Eclampsia and maternal death

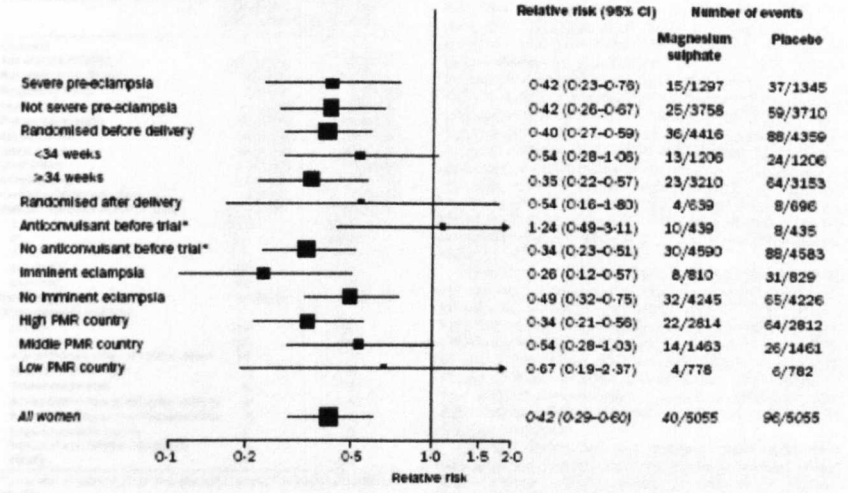


Figure 2: Effects of treatment on eclampsia

PMR=Perinatal mortality rate. *Not known whether previous anticonvulsant was given to 26 women allocated magnesium sulphate and to 37 allocated placebo.

Compliance with the allocated treatment

In both groups, 99% of women received the allocated treatment, and of these 5% also had another anticonvulsant (table 4). 16 women (eight in each group) were given the wrong pack in error: four women (two in each group) received the correct treatment, and 12 did not. All 16 women were analysed as part of the group to which they were initially allocated. 75 women were allocated an additional treatment pack, which was used for 58 women (31 magnesium sulphate, 27 placebo). 113 women (1%) did not start the allocated treatment (figure 1). The im route for maintenance therapy was used at centres in Argentina, Bangladesh, Brazil, Ghana, India, Malawi, Malaysia, Mexico, Nigeria, Pakistan, Sierra Leone, South Africa, Thailand, Uganda, and Zimbabwe. The iv route was used in Albania, Argentina, Australia, Bangladesh, Brazil, Canada, Colombia, Cuba, Denmark, Egypt, India, Israel, Italy, Jordan, Nigeria, Pakistan, Singapore, South Africa, Sri Lanka, Netherlands, United Arab Emirates, UK, USA, Venezuela, and Yemen.

For ten women treatment was unblinded, seven allocated magnesium sulphate and three placebo. Reasons for unblinding in the magnesium sulphate group were reaction to the trial treatment (six) and massive haemorrhage (one). Reasons in the placebo group were reaction to trial treatment (one), baby hypotensive (one), and possible stroke (one).

785 women (16%) allocated magnesium sulphate stopped treatment early, compared with 631 (12%) of those allocated placebo. The most common reason was the woman's request or side-effects (317 of 5055, 8%, cs 118 of 5055, 2%; table 4). Respiratory depression or absent tendon reflexes was the reason for stopping treatment for 73 of 5055 women allocated magnesium sulphate and 64 of 5055 allocated placebo. Overall, 1201 of 4999 (24%) women allocated magnesium sulphate reported side-effects compared with 228 of 4993 (5% allocated placebo (table 5). More women experienced side-effects with the im rather than the iv regimen (im 637 of 2280, 28%, cs 109 of 2273, 5%; *iv* 564 of 2719, 20%, cs 119 of 2720, 4%). Flushing, the most common side-effect, was more frequent with the im regimen (im 541 of 2280, 24%, cs 45 of 2273, 2%; *iv* 446 of 2719, 16%, cs 53 of 2720, 2%). There was little difference between the regimens for nausea or vomiting (im 61 of 2280, 3%, cs five of 2273, 0·2%; *iv* 99 of 2719, 4%, cs 13 of 2720, 0·5%). For women using the im regimen, magnesium sulphate was more likely than placebo to be stopped early (430 of 2280, 19%, cs 298 of 2273, 13%). There was little difference between the groups for the *iv* regimen (355 of 2719, 13%, cs 333 of 2720, 12%). Serious unexpected events were reported for six women allocated magnesium sulphate and three allocated placebo. For the magnesium sulphate group these were problems during the infusion (two women), fetal heartbeat stopped (one), stroke (one), cardiac arrest (one), and pulmonary oedema (one). For the placebo group they were anaphylactic shock (one), cardiac arrest (one), and stroke (one).

Outcomes

There were significantly fewer eclamptic convulsions among women allocated magnesium sulphate than among those allocated placebo (40, 0·8%, cs 96, 1·9%; ie, 11 fewer women with eclampsia per 1000 women, 95% CI 7–16 women; p<0·0001; table 6). This represents a 58% lower relative risk of eclampsia (95% CI 40–71% reduction), NNT 91 (95% CI 63–143). The NNT for women with severe pre-eclampsia was 63 (95% CI 38–181) and for those without severe pre-eclampsia it was 109 (95% CI 72–225). Excluding the 17 women reported to have possibly had eclampsia before trial entry, six of whom also had a convulsion after trial entry, makes little difference (30 of 5051, 0·8%, cs 91 of 5042, 1·8%; 57%

	Magnesium sulphate (n=5055)	Placebo (n=5055)
Outcome		
Any serious morbidity*	195 (3·9%)	183 (3·6%)
Respiratory depression	46 (0·9%)	27 (0·5%)
Respiratory arrest	5 (0·1%)	2 (0·04%)
Pneumonia	14 (0·3%)	6 (0·1%)
Pulmonary oedema	32 (0·6%)	33 (0·7%)
Cardiac arrest	4 (0·1%)	5 (0·1%)
Renal failure	49 (1·0%)	61 (1·2%)
Liver failure	52 (1·0%)	67 (1·3%)
Coagulopathy	73 (1·4%)	86 (1·7%)
Cerebrovascular accident	3 (0·1%)	6 (0·1%)
Antihypertensives after trial entry	3720 (74%)	3823 (76%)
1	2208	2182
2	1285	1383
3	174	204
>4 drugs	20	22
Unknown	32	32
Calcium gluconate	14 (0·3%)	11 (0·2%)
Other maternal problems		
Ascites	44	39
Infection	21	31
Myocardial infarction or cardiac failure	10	6
Blindness or retinopathy	6	4
Thromboembolism	4	3
Airway obstruction or laryngeal oedema	3	0
Ruptured uterus or scar or cervical tear	3)	6
Major psychiatric illness	2	5
Transient neurological symptoms	1	1
Other†	17	19

*Some women had more than one. †Includes pancreatitis, haematuria, pleural effusion.

Table 7: Secondary outcome for all women

lower relative risk, 95% CI 38–71% reduction). Overall, 3·6% (15 of 420) of women with a multiple pregnancy had eclampsia (four of 217, 2%, *vs* 11 of 203, 6%), as did 1·2% (121 of 9690) of those with a singleton pregnancy (36 of 4838, 1%, *vs* 85 of 4852, 2%). The effect on eclampsia was consistent regardless of severity of pre-eclampsia, stage of gestation at trial entry, whether an anticonvulsant had been given before trial entry, or whether the woman had delivered at trial entry (figure 2). It was also consistent regardless of parity (para=0: 27 of 2604, 1·0%, *vs* 62 of 2591, 2·4%; para 1–3: ten of 1941, 0·5%, *vs* 27 of 1896, 1·4%; para >3: three of 504, 0·6%, *vs* six of 558, 1·1%). Most women with eclampsia received non-trial magnesium sulphate after their first convulsion (115 of 136, 84%), and for 34 this drug was combined with diazepam; three women were given phenytoin.

Maternal mortality was lower among women allocated magnesium sulphate than in those allocated placebo (11, 0·2%, *vs* 20, 0·4%; relative risk reduction 45%, 95% CI −74% to 14; p=0·11). Of the women who died, one allocated magnesium sulphate also had eclampsia, as did three allocated placebo. Overall, 45% of the women who died had severe pre-eclampsia at trial entry; 39% had imminent eclampsia, 42% were less than 34 weeks' gestation, 13% were postpartum, and 19% had had an anticonvulsant in the previous 48 h. Overall, 1% of women with a multiple pregnancy died (one of 217, 0·5%, *vs* three of 203, 1·5%) and 0·3% of those with a singleton pregnancy (ten of 4838, 0·2%, *vs* 17 of 4852, 0·4%). There were no maternal deaths in low perinatal mortality countries. Maternal mortality was highest in countries with high perinatal mortality, but the relative reduction in risk was consistent (for moderate perinatal mortality countries two of 1463 maternal deaths *vs* four of 1461, relative risk 0·50, 95% CI 0·90–2·72; for high perinatal mortality countries nine of 2814 *vs* 16 of 2812, relative risk 0·56, 95% CI 0·25–1·27).

There were no clear differences between the groups in any measure of maternal morbidity, or in the composite measure of any serious morbidity (table 7). Renal failure, liver failure, and coagulopathy are closely related to pre-eclampsia, and again there was no difference (117, 2·3%, *vs* 136, 2·7%). There were no clear differences in length of stay in hospital or use of hospital resources (table 8). The analysis presented here is based on all women, but there are no substantive differences when women who died are excluded.

The most frequently used antihypertensive drugs after trial entry were methyldopa (magnesium sulphate group 2373 *vs* placebo 2439), nifedipine (1469 *vs* 1560), and hydralazine (977 *vs* 1040). 58 women were reported to have hypotension associated with trial treatment (38 *vs* 20). Around half of them had had antihypertensive drug(s) (18 of 38 *vs* 11 of 20), of which the most common were methyldopa (eight *vs* seven) and nifedipine (six *vs* four).

For women randomised before delivery, there was no clear difference in the risk of the baby dying (576, 12·7%, *vs* 558, 12·4%; relative risk increase of 2%, 95% CI −8% to 14%). This result a 0·3% in absolute risk (95% CI −1·1% to 1·6%, table 9). Excluding the 127

	Magnesium sulphate (n=4538)*	Placebo (n=4406)	Relative risk (95% CI)
Baby death			
Total	576 (12·7%)	558 (12·4%)	1·02 (0·92 to 1·14)‖
Likely in-utero death before trial entry†	57 (1·3%)	70 (1·6%)	
Baby death, excluding likely in-utero death before trial entry‡	519 (11·6%)	488 (11·1%)	1·05 (0·93 to 1·18)**
Perinatal death	518 (11·4%)	536 (11·5%)	0·99 (0·88 to 1·11)††
Stillbirth§	373 (8·2%)	364 (8·6%)	
Early neonatal death	145 (3·2%)	132 (2·8%)	
Late neonatal death	42 (0·9%)	27 (0·6%)	
Post neonatal death	16 (0·4%)	13 (0·3%)	
Infant death	0	1 (0·02%)	
Unknown	0	1 (0·02%)	
Causes of death			
Asphyxia	220	215	
Macerated stillbirth	163	168	
Prematurity¶	161	131	
Congenital malformation	15	21	
Other	14	19	
Unknown	3	4	
Still in hospital at 6 weeks	1	1	
Unknown	4	0	

*No baby for one phantom pregnancy. †Based on fetal heart beat not heard at trial entry and macerated stillbirth <24 h later. ‡n=4481 magnesium sulphate, n=4416 placebo. §For two babies allocated magnesium sulphate and one allocated placebo, the mother died before delivery. ¶Includes all liveborn babies with birthweight <2 kg, unless clearly some other cause of death. Risk difference (95% CI) is 0·3 (−1·1 to 1·6); **0·5 (−0·8 to 1·8); ††0·00 (−1·4 to 1·2).

Table 9: Baby deaths before discharge from hospital for those randomised before delivery

	Magnesium sulphate (n=5055)	Placebo (n=5055)
Stay in hospital (median, IQR) (days)*	6 (4–9)	6 (4–9)
Discharged before delivery†	200 (4%)	191 (4%)
Admission to an intensive care unit	83 (2%)	86 (2%)
Ventilated	30 (0·6%)	18 (0·4%)
Dialysis	4 (0·08%)	5 (0·1%)
High dependency area/unit		
Admission	2803 (55%)	2800 (55%)
Length of stay (median, IQR) (days)	2 (2–3)	2·0 (2–3)
Readmission	22 (0·4%)	28 (0·6%)

*For first admission only. †146 allocated magnesium sulphate readmitted for delivery, 150 allocated placebo.

Table 8: Hospital stay and use of intensive care facilities, for all women

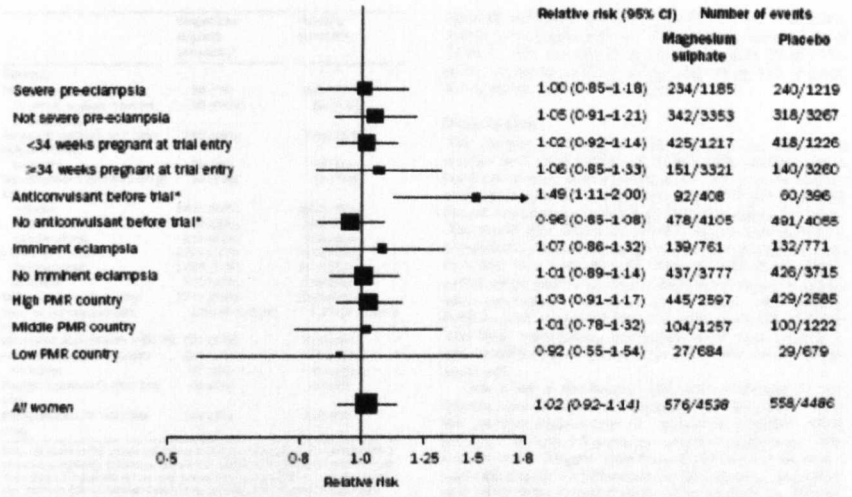


Figure 3: Effects of treatment on baby death, for those randomised before birth

PMR=perinatal mortality rate. *Not known whether previous anticonvulsant was given to two of 25 babies allocated magnesium sulphate and to seven of 36 allocated placebo.

babies likely to have died in utero before trial entry makes little difference (519, 11·6%, *vs* 488, 11·1%; relative risk 1·05, 95% CI 0·93–1·18; table 9). The effect on baby death was consistent regardless of severity of pre-eclampsia or gestation at trial entry (figure 3). The only exception is the small subgroup of women who had received an anticonvulsant before trial entry, where there appears to be an increase in the relative risk of baby death (relative risk 1·49, 95% CI 1·11–2·00). This group is the only outlying subgroup of many tested, however, a result that may well have occurred by chance. Also, mortality in this subgroup does not seem to be related to the use of magnesium sulphate before trial entry (magnesium sulphate before entry 49 of 229, 21·4%, *vs* 34 of 230, 14·8%; other anticonvulsant(s) before entry 42 of 177, 23·7%, *vs* 25 of 165, 15·2%).

These results were similar when outcome was looked at by pregnancy, taking a bad outcome as being any pregnancy in which at least one baby died (561 of 4415, 12·7%, *vs* 547 of 4359, 12·5%; relative risk 1·02, 95% CI 0·91–1·13). This includes twin pregnancies in which both babies died (12 of 168 *vs* ten of 165) and triplet pregnancies in which all three babies died (two of five *vs* none of two). Baby mortality was particularly high for women with eclampsia (six of 40, 15%, *vs* 12 of 96, 12%) and for maternal deaths (six of 11, 55%, *vs* seven of 20, 35%).

619 babies died after trial entry and before delivery (313 of 4466 *vs* 306 of 4395), excluding the 127 likely to have died before trial entry and 36 with lethal congenital malformations. Risk of death in utero after trial entry for severe pre-eclampsia was twice that for not severe pre-eclampsia (severe 132 of 1159, 11·5%, not severe 181 of 3307, 5·4%, *vs* 142 of 1187, 11·9%, *vs* 164 of 3208, 5·1%). A fifth of these stillbirths were born less than 12 h after trial entry (67 of 2092, 3·2%, *vs* 66 of 2160, 3·1%), and a third were born less than 24 h after trial entry (110 of 2839, 4·0%, *vs* 115 of 2882, 4·1%). Another third were born more than 71 h after trial entry (117 of 811, 14·3%, *vs* 119 of 802, 14·2%). For liveborn babies without a lethal congenital malformation, mortality was highest in the first week after birth and for those born before 30 weeks' gestation (table 10).

The only clear difference in outcome related to pregnancy, labour, or delivery was a lower risk of placental abruption in the magnesium sulphate group than in the placebo group (90, 2·0%, *vs* 141, 3·2%; ie, 12 fewer women with an abruption per 1000 women, 99% CI 3–21). This figure represents a 27% lower relative risk of abruption (99% CI 11–55; table 11). Of the 237 babies

	Magnesium sulphate (n=4153)			Placebo (n=4089)		
	Died 0–6 days	Died >7 days	Proportion who died	Died 0–6 days	Died >7 days	Proportion who died
Gestation at birth (weeks)						
<28	23	14	37/66 (57%)	27	9	36/67 (54%)
28–30	49	24	73/275 (27%)	35	12	47/227 (21%)
31–33	19	7	26/448 (6%)	27	9	36/474 (8%)
34–36	24	10	34/1060 (3%)	17	3	20/988 (2%)
>36	20	1	21/2290 (1%)	16	4	20/2314 (1%)
Unknown	0	0	0/15 (0%)	1	1	2/19 (11%)

Final outcome not known for 11 liveborn babies allocated magnesium sulphate and 14 allocated placebo.

Table 10: Gestation at birth and age at death for liveborn babies, without lethal congenital malformation

	Magnesium sulphate (n=4416)*	Placebo (n=4369)
Outcome		
Placental abruption	90 (2%)	141 (3%)
Of which, unclear if before or after entry	28 (0·6%)	28 (0·6%)
Antenatal steroids, in 7 days before delivery	787 (18%)	799 (18%)
Unknown	58 (1%)	59 (1%)
No information about delivery†	54 (1%)‡	41 (1%)‡
Labour		
Induced	1892 (43%)	1892 (43%)
Augmented	892 (20%)	851 (20%)
Length >8 h§	874 (41%)	922 (41%)
Caesarean section	2224 (50%)	2082 (48%)
Before labour	1486 (34%)	1373 (31%)
In labour	738 (17%)	709 (16%)
Delivery <24 h after entry	2797 (63%)	2863 (66%)
Entry to delivery (median, IQR) (h)¶	12·5 (4·5–33·9)	11·3 (4·2–32·0)
Blood loss after delivery >500 mL	750 (17%)	774 (18%)
Manual removal of placenta	148 (3%)	162 (4%)
Unknown	57 (1%)	54 (1%)
Platelet transfusion after trial entry	38 (1%)	38 (1%)
Blood transfusion after trial entry	224 (5%)	242 (6%)

Data are number (%) unless otherwise indicated. *Excludes one woman with a phantom pregnancy. †Includes two women allocated magnesium sulphate and three allocated placebo where only information about delivery is whether baby was liveborn. ‡Three women died before delivery; two allocated magnesium sulphate, one allocated placebo. §n=2135 magnesium sulphate, n=2228 placebo had a vaginal delivery. ¶Five women allocated magnesium sulphate had vaginal delivery for twin one and a caesarean section for twin two. ||Only for those not discharged before delivery.

Table 11: Outcomes relevant only to women randomised before delivery

from these pregnancies, a third died (33 of 93, 35·5%, cf 52 of 144, 36·1%). There was also a 5% higher risk of caesarean section, which was borderline for significance at the 1% level (relative risk 1·05, 99% CI 1·00–1·11, p=0·02). There were no clear differences in any measure of neonatal morbidity (table 12). The analysis presented here is based on all babies, but the only difference when liveborn babies who died are excluded is that a smaller proportion was ventilated (110 of 3059, 3%, cf 96 of 3024, 2%).

Overall, centres using the im maintenance regimen had a higher risk of eclampsia and of baby death than those using the iv regimen. However, there was no evidence that route of administration influenced the effectiveness of magnesium sulphate compared with placebo. For the im regimen: eclampsia 20 of 2301, 0·9%, versus 54 of 2292, 2·4%; baby death 380 of 2171, 17·5%, versus 368 of 2159, 17·0%. For the iv regimen: eclampsia 20 of 2754, 0·7%, versus 42 of 2763, 1·5%; baby death 197 of 2367, 8·3%, versus 190 of 2327, 8·2%.

	Magnesium sulphate (n=4162)	Placebo (n=4096)
Birthweight (g)*		
<1500	753 (17%)	707 (16%)
<2500	2256 (50%)	2177 (49%)
Apgar <7 at 5 min	235 (6%)	227 (6%)
Intubated at place of delivery	175 (4%)	171 (4%)
Cerebral ultrasound imaging	322 (8%)	317 (8%)
Abnormal ventriculomegaly	28	25
Persistent parenchymal echogenicity	31	28
Neonatal convulsion(s)	40 (1·0%)	52 (1·3%)
Length of stay in hospital (median, IQR) (days)	5 (3–9)	5 (3–9)
Admission to special care baby unit	1629 (39%)	1591 (39%)
In special care baby unit >7 days	810 (19%)	783 (19%)
Death or in special care baby unit >7 days*	1330 (29%)	1302 (29%)
Ventilation	389 (9%)	359 (9%)

Data are number (%). *n=4538 magnesium sulphate and n=4486 placebo, total births.

Table 12: Neonatal morbidity for liveborn babies of women randomised before delivery

Discussion

The Magpie Trial was designed to assess the effects, on women and their babies, of magnesium sulphate when used for women with pre-eclampsia. To provide reliable evidence to guide the care of women with pre-eclampsia the trial needed to recruit very large numbers of women. The study also aimed to provide results that would be generalisable to a wide range of clinical settings, in both rich and poor countries. In order to achieve our target recruitment, and to include collaborators from developed and developing countries, the protocol was simple, flexible, and integrated into the existing health services. The high compliance, completeness of data collection, and breadth of the collaboration reflect the success of this approach.

This study is the largest trial ever conducted for the hypertensive disorders of pregnancy. 12 times larger than the previous biggest trial of magnesium sulphate versus placebo,[2] it took 3·5 years to complete recruitment. The success of the Magpie Trial hinged critically on the active and enthusiastic collaboration of obstetricians, midwives, and other busy hospital staff, often working in difficult circumstances in many low-middle income countries. These researchers endorsed the concept that it is not ethical to continue to use an unproven treatment if the opportunity arises to assess the safety and effectiveness of that intervention in a rigorous and unbiased fashion.

Results from the Magpie Trial demonstrate clearly that magnesium sulphate is effective in considerably reducing the risk of eclampsia for women with pre-eclampsia. Overall, 11 per 1000 fewer women allocated magnesium sulphate had an eclamptic convulsion. Despite the inevitable reduction in power of a subgroup analysis, the results were consistent regardless of the severity of pre-eclampsia at trial entry or whether treatment was before or after delivery. The relative reduction in risk was also consistent across low, middle, and high perinatal mortality countries. Combining data from the Magpie Trial with those from the earlier systematic review[1] makes little change to the results presented here. For eclampsia, the combined relative risk is 0·41 (95% CI 0·29–0·58). The trend in maternal mortality also favoured magnesium sulphate, although a small increase in mortality has not been excluded.

One of the concerns about magnesium sulphate has been the risk of respiratory depression. Although in this study more women allocated magnesium sulphate had respiratory depression or respiratory arrest, the actual numbers were small, and there was no overall difference in serious maternal morbidity. Similarly, there was no clear difference in ventilation for the babies of women randomised before delivery. However, a quarter of women allocated magnesium sulphate had unwanted side-effects, compared with 5% allocated placebo. 8% also had problems at the injection site, compared with 4% allocated placebo. Although very few of these side-effects were life threatening, most of them were unpleasant and many women experienced multiple side-effects. Hence, the higher number of women allocated magnesium sulphate who stopped treatment early. Although there is no evidence that effectiveness is influenced to a clinically important degree by the choice of regimen, the iv route for maintenance therapy does appear to be associated with

fewer problems. Nevertheless, the decision about which regimen to use is likely to be influenced by a range of other factors, including cost, availability of trained staff, and safety. The apparent reduction in problems may anyway be related more to the higher dose of the im regimen, than to any difference per se.

These comparisons between women who received the iv rather than the im regimen should be interpreted with caution, as the route for maintenance therapy was not allocated at random.

The Magpie Trial aimed to assess the effects of magnesium sulphate for the child, as well as the mother. One of the beliefs supporting the unevaluated use of magnesium sulphate over many decades has been that it improves outcome for the child. Recent support for this belief has come from case-control studies, suggesting that in-utero exposure to magnesium sulphate might reduce the risk of cerebral palsy for low birthweight (<1500 g) babies.[21] However, there is also concern that magnesium sulphate exposure for these vulnerable babies might be associated with an increased mortality.[22] Data presented here suggest that, overall, there is little or no effect on mortality, although a small increase or decrease has not been excluded. The small subgroup of babies exposed to an anticonvulsant before trial entry do appear to have an increased mortality in the active group, but these deaths were not restricted to those who had received magnesium sulphate before randomisation. This apparent difference may reflect the play of chance. We observed a reduction in the risk of placental abruption, but this is not reflected in any effect on total mortality for the baby. There was no evidence of a difference in any other measure of neonatal morbidity. In particular, there was no evidence of a difference in the predefined outcome of death or in a special care unit for more than 7 days. We now need reassurance that there are no adverse consequences for the child's later development. Follow-up of a proportion of the children whose mothers were recruited to the Magpie Trial is underway.

There was little evidence to support the hypothesis that magnesium sulphate, administered according to the regimens in this trial, might be useful either as a tocolytic or an antihypertensive agent. The small (5%) increase in the relative risk of caesarean section is supported by data from the systematic review.[4] As there is no evidence of an effect on induction of labour, length of labour, blood loss at delivery, or retained placenta this increase may be related to other factors. Similarly, there was no clinically useful reduction in the use of antihypertensive drugs. There has been concern, based on just a tiny number of case reports,[23,24] about severe hypotension related to the simultaneous use of magnesium sulphate and nifedipine. In the Magpie Trial, 30% of women received nifedipine after trial entry and no associated adverse events were reported. For the few women who did have hypotension there was no association with the combination of nifedipine and magnesium sulphate.

Although the trial was placebo controlled, it is possible that the occurrence of side-effects allowed the allocation to be guessed for about one-fifth of women allocated magnesium sulphate. It is unlikely that this would have substantially influenced the assessment of outcome, as the main outcome measures were objective.

The aetiology of pre-eclampsia and eclampsia remains elusive. Exactly how magnesium sulphate might control eclamptic convulsions is also unclear. Magnesium may have a localised cerebral effect. For example, it may cause vasodilatation with subsequent reduction of cerebral ischaemia,[25] and/or block some of the neuronal damage associated with ischaemia.[26,27] A possible mechanism for vasodilatation is relaxation of smooth muscle. That magnesium may have a generalised effect on all smooth muscle, including the peripheral vasculature and uterus, has also been suggested. Hence the hypotheses that it may have antihypertensive and tocolytic effects. This generalised effect now seems unlikely. Alternatively, any effects of magnesium sulphate in control of eclamptic convulsions may be, wholly or part, through its role as a blocker of N-methyl-D-aspartate receptors in the brain.[26] These receptors are activated in response to asphyxia, leading to calcium influx into the neurons, which causes cell injury. It is suggested that magnesium may block these receptors, so reducing calcium influx and protecting the neurons from damage.[26,27]

An unexpected finding was that so few of the women who died had had eclampsia. A possible explanation is that magnesium sulphate may also have beneficial effects on other organs implicated in pre-eclampsia, a suggestion supported by the reduction in placental abruption. Fewer women allocated magnesium sulphate rather than placebo had renal failure, liver failure, or coagulopathy, but the difference was small and could have occurred by chance. Pre-eclampsia is associated with endothelial dysfunction.[28] Magnesium sulphate may somehow improve local perfusion by improving endothelial function or microvascular perfusion.

Magnesium sulphate is remarkably effective at reducing the risk of eclampsia, whether this is the first seizure or recurrence of convulsions.[29] In the Magpie Trial, as in the Collaborative Eclampsia Trial,[29] management of the acute convulsion was with magnesium sulphate. It has been argued that diazepam should be used for treatment of the actual convulsion.[30] There is no evidence to support this suggestion. Data from the Magpie Trial present further evidence that magnesium sulphate alone should be used for women with eclampsia: both to control the seizure and to prevent recurrence.

Magnesium sulphate was little used in many countries, including the UK, before the results of the Collaborative Eclampsia Trial were published in 1995.[29] This situation arose partly because of concerns about respiratory depression in the mother. The Magpie Trial has further dispelled these concerns. Importantly, safe monitoring was achieved without serum magnesium measurement, using simple clinical assessment of tendon reflexes, respiratory rate, and urine output. This achievement has obvious implications for care, particularly in low-income and middle-income countries.

Two magnesium sulphate regimens were used in this trial. Both are widely used in clinical practice and both were also used in the Collaborative Eclampsia Trial.[29] At the dosages and duration of treatment used here magnesium sulphate is both safe and effective in preventing eclampsia in women with pre-eclampsia. Whether or not a higher dose regimen, as has been argued for,[31] would be more effective is unclear. But, as the size of the risk reduction reported here was so large, this seems unlikely. Higher doses are unlikely to be safer, even if they are more effective. The reassurance about safety for both woman and child from these data cannot be extrapolated to higher doses, or to a longer duration of treatment.

The Magpie Trial Collaborative Group involved a wide range of people from four continents with a common interest in improving the care of women with pre-eclampsia. Results from this study confirm the high morbidity and mortality associated with this devastating condition. Outcome was particularly poor for women with

severe pre-eclampsia, and those from high perinatal mortality countries. We did attempt to subdivide the women without severe pre-eclampsia, based on blood pressure and proteinuria at randomisation. Although this successfully distinguished women with low and intermediate mortality for the baby, the relative risk of eclampsia changed little. 85% of recruitment to the Magpie Trial was from low-middle income countries, where the risk of eclampsia, maternal death, and baby death were highest. Magnesium sulphate is the drug of choice for eclampsia, but is not easily available in some countries.[6] To ensure that women recruited to the trial had optimum care if they developed eclampsia, we provided some collaborators in Africa and Asia with extra magnesium sulphate. Having now shown that magnesium sulphate also benefits women with pre-eclampsia, removing barriers in the supply and use of magnesium sulphate should be a priority for those responsible for maternal health services in developing countries, including international agencies such as the United Nations Population Fund (UNFPA), the United Nations Children's Fund (UNICEF), and WHO.

Implications for clinical practice

The results of this trial should be made available to women with pre-eclampsia, and those responsible for their care. Magnesium sulphate should be considered for women with pre-eclampsia for whom there is concern about the risk of eclampsia. As it is an inexpensive drug, it is especially suitable for use in low-income countries. *iv* administration is preferable, where there are appropriate resources, as side-effects and injection-site problems seem lower. Duration of treatment should not normally exceed 24 h, as the reassurance about safety applies only to the regimens used in this trial. Serum monitoring is not necessary. Administration and clinical monitoring of magnesium sulphate can be done by medical, midwifery, or nursing staff, provided they are appropriately trained.

This trial included women only after admission to hospital. Whether a loading dose of magnesium sulphate should be used for women at primary-care level before they are transferred to hospital is unclear. Other factors in this decision are likely to include how long it will take to get the woman to hospital, the support that is available during transfer, and severity of her pre-eclampsia.

Implications for research

Remaining questions about the use of magnesium sulphate include: what is the minimum effective dose? When is the optimal time to give it? Should it be used at primary-care level for women being transferred for secondary or tertiary care? What are the long-term consequences of exposure for the mother and her child? Many clinicians reserve magnesium sulphate for women for whom delivery is planned in the next 24 h. In the Magpie Trial some women were given 24-h treatment and the pregnancy was allowed to continue, if preterm and stable. Few of these women had any further treatment with magnesium sulphate.

Additional research is continuing on the long-term follow-up of a proportion of the women and children in the Magpie Trial, and on the cost implications of the findings for a range of settings.

Conclusions

Magnesium sulphate reduces the risk of eclampsia, and it is likely that it also reduces the risk of maternal death. At the dosage used in this trial it does not have any substantive harmful effects on the mother or child, although a quarter of women will have side-effects.

Magpie Trial Collaborative Group

Central Coordinating Team—Lelia Duley (clinical coordinator), Barbara Farrell (trial manager), Patsy Spark (trial programmer), Barbara Roberts (trial secretary), Karen Watkins (research fellow, May, 1998, to July, 1999), Leanne Bricker (research fellow, August, 1999, to April, 2000), Liza Wang (data manager, from November, 1999), Nina Armstrong (assistant to trial manager, until November, 2000), Mary Tynan (assistant to trial manager, from November, 2000), Naleem Saih (data assistant, January, 2001, to March, 2002), Anna Hunt (data assistant January, 2001, to February, 2002), Rebecca Smyth (research midwife, from July, 1999), Sarah Cooper (research midwife, July, 1999, to December, 2000), Amanda Wilson (research midwife, July to October, 1999), Ursula Bowler (trial coordinator, January, 1998, to June, 1998), Jane Norman (trial coordinator, September, 1998, to October, 1999).

Coordinating Team (for Spanish-speaking countries in Latin America)—Edgardo Abalos (clinical coordinator), Fernando Bunguetto (data assistant), Liana Campodonico (data manager), Guillermo Carroli (CREP director), Daniel Giordano (Programmer), Bernise Carroli (secretary), Roberto Lede (IAMBE Coordinator), Pablo Copertari (IAMBE data assistant).

Coordinating Team (for South Africa)—Jack Moodley (clinical coordinator), Vanessa Tombe (secretary), Gugulethu Ndlovu (coordinator, South Africa, until December, 2000), Nelisiwe Mngoni (coordinator, South Africa, from January, 2001).

Statistical support—David Smith, Douglas Altman (Centre for Statistics in Medicine, Oxford).

Trial Steering Committee—Douglas Altman (trial statistician, from September, 2001), Rory Collins, Lisa Cotterill (observer), Lelia Duley (trialist), Barbara Farrell (trialist), Edmund Hey (until November, 2000), Anna Karaoglou (observer), Marian Kelly (observer), Richard Lilford, James Neilson (trialist), Stephen Robson, Peter Rubin (chair), David Smith (trial Statistician, until September, 2001), James Thornton, Sara Twaddle, Jose Villar (observer), Isabel Walker.

Management Group—Douglas Altman (from September, 2001), Mike Clarke, Lelia Duley, Barbara Farrell (chair), Alastair Gray (from November, 2001), Edmund Hey (from December, 2000), James Neilson, David Smith (until September, 2001), Patsy Spark.

Data monitoring and ethics committee—Richard Doll (chair), Adrian Grant, Nazir Patel, Jimmy Volmink, Godfrey Walker.

Writing Group—Douglas Altman, Guillermo Carroli, Lelia Duley (chair), Barbara Farrell, Jack Moodley, James Neilson, David Smith.

Collaborators by country (total number of women recruited)—*Albania* (114): Maternité Pogradec (1): R Pere; Maternity Hospital No 1 (1): S Balili, M Gjoni, G Theodhosi; Maternity Hospital No 2 (108): A Bimbashi, E Demalia, O Glicitheni, R Moisiu; Maternity of Burrel (4): O Kadiu, H Kloni; *Argentina* (1638): Hospital Carlos A Durand (55): A Kanofinski, R Papera, M Pesaresi, M Sueldo; Hospital Del Centenario (45): W Barbato, L Bloise, F Candio, A Casella; Hospital Eva Perón (105): L Mignini, S Mirkin, G Strada Saenz; Hospital Interzonal Dr Jose Penna (250): M Botin, J Castaldi, Y Partida; Hospital Isidoro G Iriarte (22): H Blanco, L Cipriano, S U Posenato, N Torregiani; Hospital J B Iturraspe (36): G Koch, M López Candioti, L Ostertag, S Senn; Hospital Jose Maria Cullen (56): C Arias, M Bunos, G Kerz; Hospital Juan R Vidal (102): G Abreo, J Acosta, L Ayala, C Casella; Hospital Maternidad Martin (105): M Menighini, J Nardin, M Perotti; Hospital Nacional Professor Alejandro Posadas (160): E Candit, A Ferreiros, M Palermo, S Varela; Hospital Provincial Santa Fe (30): B Arregui, H Delprato, J Di Benedetto, D Fernandez; Hospital Regional 'Dr Ramon Carrillo' (150): R Abalos Gorostiaga, M Costas, M Curioni; Hospital Rivadavia (2): M Moreno; Hospital Roque Saenz Peña (20): A Ceballos, E Ludmer, C Solis, R Quiroga; Luis Carlos Lagomaggiore (44): M Kemelmajer, R Martin, W Massa; Maternidad Provincial Salta (Nuevo del Milagro) (132): M Canares, M Lezcano; Materno Infantil "Ramón Sardá" (114): E Andiru, M Estiú, C Rossi, E Ulens; Materno Provincial Córdoba (64): D Cofone, Z Maldonado, G Morales, B Ortiz de Speranza; Zonal de Agudos "Heroes de Malvinas" (65): J Antoni, M Damiano, E Dos Santos; *Australia* (150): Ballarat Health Services (5): I Mayes; Box Hill Hospital (20): B Eldridge, M Wong; Dandenong Hospital (8): R Burrows, T Nash, J Stratton; Royal Women's Hospital (42): P Colditz, C Portman, M Pritchard; Shoalhaven District Memorial Hospital (4): B Hoolahan, I Hoult, P Paris-Browne; The Queen Elizabeth Hospital (2): W Hague, B Pridmore; The Townsville Hospital (50): A Dederer, S Hammond, D Watson; Women's and Children's Hospital (5): C Crowther, J Dodd, M Morton; *Bangladesh* (200): Bangabandhu Sheikh Mujib Medical University (23): Ashrafunnesa, N Begum, S Chowdhury, L Shamsuddin; Lamb Hospital (160): B Debnath, C Edwards, J Ferdous, F Mussel; Memorial Christian Hospital (17): T Hepworth; *Brazil* (161): Hospital das Clínicas Da UFPE (44): E Alves Moreira, C Barros Santos, S Freire, C Salles Lette; Hospital das Clinicas de Botucatu (11): J Abbade, I Calderon, J Peracoli, M Rudge; Hospital Maternidade Leonor Mendes de Barros (4): A Atallah, M Duarte-Barros, V Tadini, E Viana; Hospital Materno Infantil de Goiânia - GO (8): L Schvartz, G Souza, A Vidal, M Viggiano; Maternidade Escola Januário Cicco (94): A Araujo,

H Nóbrega, T Nóbrega de Oliveira, C Pinheiro; *Canada*: Sainte Justine Hospital (40): N Michon, F Morin, E Bey; Cotonou (481): Clinica Materno Infantil "Los Farallones" (80): J San Madribán; Fundación Clínica Valle del Lili (240): E Cobo; Universidad Nacional de Colombia, Hospital Materno Infantil de Bogotá (77): A Bautista, H Cainin, C Camón; Hospital Universitario de San Ignacio (78): J Ardila, L Cuervo, J Lozano, M Rojas; *Cuba* (261): Docente Gineco-Obstetrico "Eusebio Hernandez" (117): A Bosa, A Garcia, R Miras; Hospital Gineco-Obstetrico "Americo Arias" (141): M Alcalde Dueñas, U Farnot Cardoso, E Gómez Sosa, G Peñate; Hospital Provincial Gineco-Obstetrico Julio Alfonso (3): R Landeta, I Montesino, G Ponce; *Denmark* (34): Gloserup Hospital (2): H Nyholm, J Svarc; Hillerod Sygehus (2): N Moller; Odense University Hospital (27): A M Holm, B Sorensen; Skejby Hospital (5): K Stajas; *Egypt*: Assiut University Hospital (108): T Al-Hussaini; *Ghana*: Komfo Anokye Teaching Hospital (117): K Danso, E Kwapong, F Ofosu-Barko, O Oturuye; *India* (719): Christian Medical College Hospital (570): M Padmini Jasper, G Korula; J N Medical College AMU (12): R Sharma; King Edward VII Memorial Hospital_Mumbai (206): M Bhamcharyya, A Chauhan, V Raut; Maulana Azad Medical College and Lokenayak Hospital (42): A Mathai-Rathore; SAT Hospital, Medical College Trivandrum (68): S Balakrishnan; Shree Maharani Shantadevi Hospital (21): P Vadakkepat; *Iraq*: Poriya Hospital (4): M Ben-Ami, Y Perlin; *Iraq* (44): OIRM Sant'Anna (4): E Gollo, A Maina; Valduce Hospital (40): M Lovotti; *Jordan*: Jordan University Hospital (29): M Amr; Mawet Queen Elizabeth Central Hospital (112): J D Chipangwi, V M Lema, L A R Mdmavulya.; *Malaysia* (34): Hospital Universiti Kebangsaan Malaysia (13): N Adzeb, H Dali, Z Mahdy; Seremban Hospital (21): R Jeyaseelly, M Krishnasamy, S Paramasivam, S Teh; *Mexico*: Hospital Civil de Guadalajara "Dr Juan I Menchaca" (67): S Fajardo-Dueñas, J González-Moreno, MS Rojo-Tello, FG Sandoval-Batta; *Nigeria* (401): Ade Maternity Home and Clinic (7): T Fatoyo; Medytop Hospital (7): O Oduneye; Nigerian Security Printing and Minting Staff Hospital (12): Y Kayode, I Maduegbuna; Ogun State University Teaching Hospital (18): A Olanrin, A Sule-Odu; Sacred Heart Hospital (9): O Akande, G Beenack, L Enobebe, M Obodua, H Oshinyemi; State Hospital (14): A Ayinde; University College Hospital (279): B Adesina, I Adewole, K Afolabi, A Oladokun; University of Port Harcourt (58): C Akani, N Inimgba, C John; Usmanu Danfodiyo University Teaching Hospital (73): B Ekele, Y Isah; Victory Hospital (14): A Akindele; *Pakistan* (298): Jinnah Post Graduate Medical Centre (44): R Jamelle; Lady Reading Hospital (70): N Ruby Faiz, F Gul, S Noor; Maternal and Child Health Centre, Islamabad (180): G Mahmud, S Serwar, N Tasnim, A Younus Khan; *Sierra Leone*: Princess Christian Maternity Hospital (37): S Cassama, T George, D Lavaly, I Lakuley; *Singapore* (46): KK Women's and Children's Hospital (13): A Siow, KH Tan, GSH Yeo; Singapore General Hospital (33): D Karalingam, A Tan, HK Tan, LK Tan; *South Africa* (2680): Addington Hospital (20): A Czarnocki, J Devjee, M Rajagopal; Chris Hani Baragwanath Hospital (95): E Buchmann, N Pirani; Coronation Hospital (130): G J Hofmeyr, C Nikodem, C Parker, L Thomas; East London Complex (170) (Cecilia Makiwane Hospital (94); Frere Maternity Hospital (76)): S Ferreira, G J Hofmeyr, L Maregesi, A Roodt, M Singata; Kalafong Hospital (754): R Mokhondo, R Pattinson, R Prinsloo; King Edward VIII Hospital (535): M Adhikari, N Mngoni, J Moodley, G Ndlovu; Mankweng Hospital (68): K Jackson, S Kamburan, R Mahapaya, P Mohlala; Medunsa Hospital (172): N Madurro, L Matseli, E Mokgadiong.; Pelonomi Hospital (50): R Bam, M Schoon; Pretoria Academic Maternity Hospital (256): T Fouche, P Macdonald, R Richardson, H Taljaard; Tygerberg Hospital (423): E Carstens, H Odendaal, W Steyn; *Sri Lanka* (11): North Colombo Teaching Hospital (7): S Fernando; Teaching Hospital (4): J Amarasinghe, A Samarasanga; *Thailand* (20): Maternal and Child Hospital (Khon Kaen) (8): N Winiyakul, A Wongrechaawat; Srinagarind Hospital (8): P Lumbiganon, J Thinkhamrop; Udornthani Hospital (4): T Jirakunsomchok, S Panichkam, M Songthamwat, S Thuiert; *The Netherlands*: Medisch Centrum Rijnmond-Zuid, locatie Clara (52): J Duvekot; *Uganda* (605): Mulago Hospital (555): F Mirembe, F Mirairo, R Nakayira, I Namagembe; St Francis Hospital Nsambya (50): R Byaruhanga, P Okong; *United Arab Emirates*: Corniche Hospital (7): M El-Sheikh, S Wani; *UK* (604): Aberdeen Maternity Hospital (12): D Campbell, P Duncliean, I Gilbert; Bilinge Hospital (3): R El Gawly; Birmingham Womens Hospital (7): M Goulding, M D Kilby, P J Thompson; Bradford Royal Infirmary (32): D Jankowicz, D Tuffnell; Castle Hill Hospital, Cottingham (11): G Fawcett, A Hill; Central Middlesex Hospital (1): S Kerslake; Chelsea and Westminster Hospital (8): D Williams; City Hospital NHS Trust, Birmingham (1): M Luckas, A Pirie; Colchester General Hospital (4): S Colerun, Y El-Hallaq, J Vince; Countess of Chester NHS Trust (17): K Grimes, M McCormack, J McMahon, C Sales; Cumberland Infirmary (10): J Durham, R Lawley; Derby City General Hospital (7): A Fowlie, A Hoobin; Dr Gray's Hospital, Elgin (4): S Campbell, D Evans, N Maclean, I Oborocha; Friarage Hospital, Northallerton (4): M Kumarendran; Gloucestershire Royal Hospital (7): M Read, A Thornberry; Good Hope Hospital, Sutton Coldfield (22): D Churchill, D Roper; Hammersmith Hospital NHS Trust (2): L Fusi; Hope Hospital, Salford (3): A Niland, A Raiken; Hull Maternity Hospital (29): A Legge, S Lindow, J Tuson; Ipswich Hospital NHS Trust (7): J Burrows, G Davies, S Patient, J Watts; Kingston Hospital NHS Trust (1): A Mosling, M Turner; Leeds General Infirmary (34): L Holt, G Mason, J Thornton, J A Wright; Leicester General Hospital (15): S Hodgett, I Szalamonn, E Wood; Leicester Royal Infirmary (16): C Blackwell, P Bovis, J Waugh; Leighton Hospital, Crewe (6): M Luckas, M Magee, L Tomlinson, L Toner; Lister Hospital, Stevenage (1): D Salvesen; Liverpool Women's Hospital (54): L Bricker, L Campbell, L Dinardo, S Quarby; Mater Hospital, Belfast (2): J Devlin, R Hearty, O Macleod, H Sidhu; North Middlesex Hospital (2): A Govind; North Staffs Maternity Hospital (44): R Johanson, L Lucking, B Whittingham, P Young; North Tees General Hospital (20): J Jones, J Macaulay, J Mackie, J Mason; Northern General Hospital, Sheffield (1): P Stewart; Northwick Park Hospital, Harrow (3): J Spencer; Ormskirk General Hospital (7): P Hendy-Ibbs; Princess of Wales Hospital, Bridgend (4): S Hardy, P Morris; Queen Charlotte's And Chelsea Hospital (20): M de Swiet, N Jackson, S Paterson-Brown, V Springer; Queen Elizabeth The Queen Mother Hospital, Margate (4): P Belgaumkar; Queen Mary's Hospital, Sidcup (10): R Smith; Queen's Part Hospital, Blackburn (14): A Hart, C Schram; Royal Bolton Hospital (13): K Bancroft, N Johnson; Simpson Memorial Maternity Pavilion, Edinburgh (28): A Barwick, S Cowan, K Dundas, R Hughes; Royal Lancaster Infirmary (3): D Burch, M Parker; Royal Maternity Hospital, Belfast (3): D McKenna; Royal Surrey County Hospital (2): R Hurt, A Kerr, K Morton, S Whitcroft; Royal Sussex County Hospital (22): R Bradley, S Purdy; Royal United Hospital, Bath (21): S Collins, N Johnson, F Jones, H Jones; Royal Victoria Infirmary, Newcastle-upon-Tyne (16): S Robson; Singleton Hospital (9): J Dibby, S Butcher; South Cleveland Hospital (27): M Hogg, S Hutchison, K Lincoln; Southern General Hospital, Glasgow (25): S Pringle, J Vandermonen; St James' University Hospital, Leeds (12): J Tucker, J Walker, A Wright; St Mary's Portsmouth (10): V Osgood; St Michael's Hospital, Bristol (7): F Anderson, C Domagala, M Mills, A Tizard; St Peter's Hospital, Chertsey (2): S Newbold, S Winston; Stepping Hill Hospital, Stockport (5): C Candelier, H Scanlon, S Titterington; Stoke Mandeville Hospital NHS Trust (3): D Clairmonte, I Currie, B Prosser; Sunderland Royal Hospital (54): H Cameron, S Stelling, T Wake; Tameside General Hospital (7): J Evans, B Hamerseley, K McGillivary, A Watson; The Jessop Wing (10): F Fairlie, S Lazenby; The Rosie Hospital, Cambridge (13): G Hackett, C Patient, R Sherwing, S Smith; University College Hospital, London (1): P Meller, R Malnycznik, P O'Brien, A Yansen; University Hospital Aintree (36): E Burke, G Shaw; University Hospital Lewisham (10): P Knott, E Peregrine, J Ross; West Cumberland Hospital (3): S A Bober; Wordsley Hospital, Stourbridge (6): M Troth, A Warwick; Wycombe General Hospital (1): D Eustace; Ysbyty Gwynedd (2): L Bolton; *USA*: OHSU Hospital (47): S-L Jacobson; *Venezuela*: Maternidad Concepcion Palacios (84): F Febres, A Mejias; *Yemen*: El Sabeen Maternity and Child Hospital (112): N Al-Sarimi, I Asharebi, A El-Rabee, A Ghorab; *Zimbabwe*: Harare Hospital (612): E N Hammond, K Mahomed, L Masangaise.

Conflict of interest statement

None declared.

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Appendix 2

«Centre_ID»

13 May 2008

«Woman_Given_name» «Woman_Family_Name»
«Address_Line_1»
«Address_Line_2»
«Address_Line_3»
«Address_Line_4»
«Postcode»

Dear «Woman_Given_name»

Although it was some time ago now, I am sure you will remember that during your recent pregnancy your doctors became concerned that you were developing signs of pre-eclampsia (toxaemia). The hospital where you were being cared for was one of many testing to see if treatment with magnesium sulphate was helpful in controlling that condition, and you were good enough to agree to help with this study (the Magpie Trial).

We have already collected a lot of information on the short term effects of such treatment, but before this comes into more general use we also need to be sure about your current health and that of your child.

Enclosed are two short questionnaires. We would be grateful if you could complete as much of them as you can. Please return them to us in the prepaid envelope provided.

All the information collected will be confidential and used only by the researchers working on the study.

If you want to ask questions, or know more, before completing these questionnaires, please do not hesitate to contact Rebecca at the telephone number below. Leave a message on the answer machine if nobody answers, and Rebecca will get back to you.

Thank you in advance for your help.

Yours sincerely

Rebecca Smyth (Tel: 0151 702 4110)
Research Midwife

Lelia Duley
Clinical Co-ordinator

Encs.

If you do NOT wish to be contacted again, please tick the box and return this letter in the prepaid envelope provided. ☐

The Magpie Trial is funded by the Medical Research Council, Department for International Development, World Health Organisation and European Commission

Clinical Co-ordinator: Lelia Duley. Trial Manager: Barbara Farrell

happy
birthday

from
MAGPIE

24B

Parent's questionnaire

For children aged around 24 months

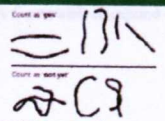
We would like to ask you some questions about your child's health and progress. Please tick the most appropriate box against each question, giving further details where requested. If you need more space, please write at the end of the questionnaire, referring to the question by number.

Child's name: **Date of birth:**

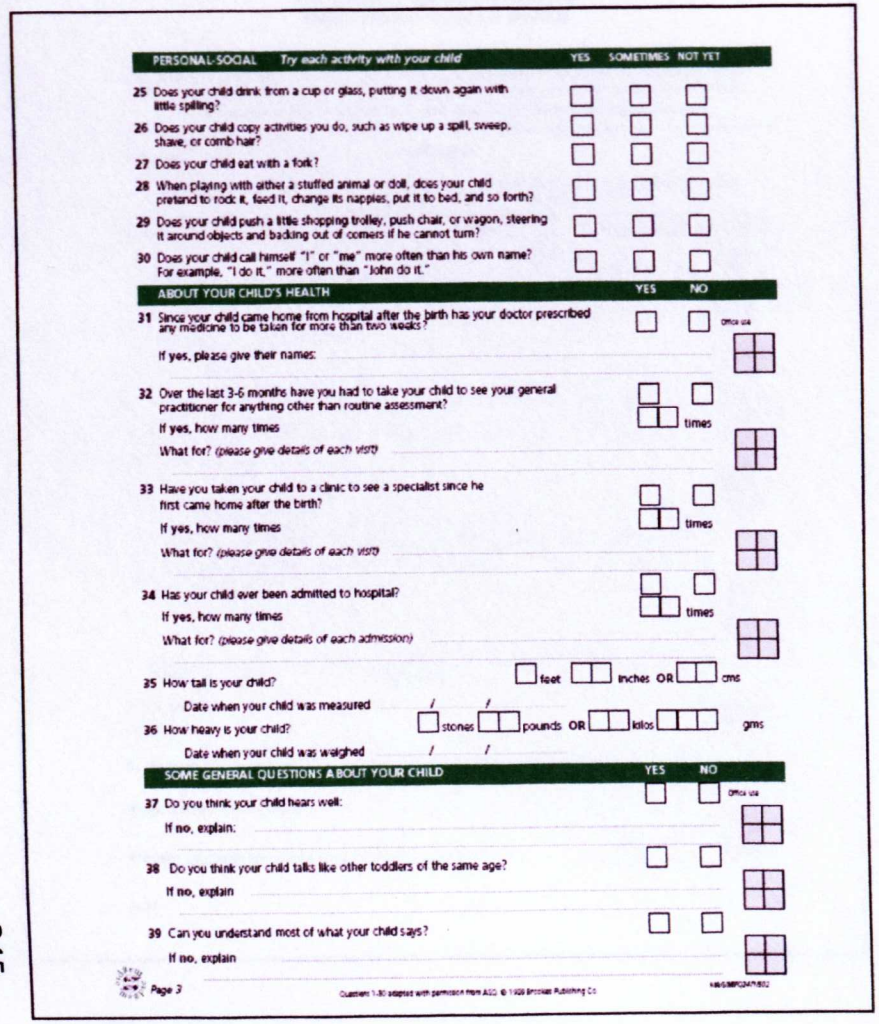
If you would like to talk about any of these questions, please contact Rebecca Smyth (details at end of questionnaire) or ask your health visitor or GP if they can help you. The information you give us will be confidential, and used only by the researchers.

Questions 1-30 ask about activities children do. Your child may already have done some of the things described here, and there may be quite a few your child is not yet doing. For each question, please tick the box that says whether your child is doing the activity regularly, sometimes, or not yet. At this age, many children may not be cooperative when asked to do things. You may need to try the following activities with your child more than once. If possible, try the activities when your child is cooperative. If your child can do the activity but refuses, tick 'Yes' for the question.

COMMUNICATION *Try each activity with your child*	YES	SOMETIMES	NOT YET
1 Without showing him first, does your child point to the correct picture when you say, "Show me the cat" or ask, "Where is the dog?" *(He needs to identify only one picture correctly.)*	☐	☐	☐
2 Does your child imitate a two-word sentence? For example, when you say a two-word phrase, such as "Mummy eat," "Daddy play," "Go home," or "What's this?" does he say both words back to you? *(Tick 'Yes' even if his words are difficult to understand.)*	☐	☐	☐
3 Without giving him clues by pointing or using gestures, can your child carry out at least three of these kinds of directions? a. "Put the toy on the table." b. "Close the door." c. "Bring me a towel." d. "Find your coat." e. "Take my hand." f. "Get your book."	☐	☐	☐
4 If you point to a picture of a ball *(cat, cup, hat, etc.)* and ask your child, "What is this?" does he correctly name at least one picture?	☐	☐	☐
5 Does your child say two or three words that represent different ideas together, such as "See dog," "Mummy come home," or "Cat gone"? *(Don't count word combinations that express one idea, such as "Bye-bye," "All gone," "All right," and "What's that?")*	☐	☐	☐
Please give an example of your child's word combinations:			
6 Does he correctly use at least two words like "me," "I," "mine," and "you"?	☐	☐	☐
MOVEMENT SKILLS *Try each activity with your child*	**YES**	**SOMETIMES**	**NOT YET**
7 Does your child walk down stairs if you hold onto one of his hands? *(You can look for this at a shop, in a playground, or at home.)*	☐	☐	☐
8 When you show him how to kick a large ball, does your child try to kick the ball by moving his leg forward or by walking into it? *(If he already kicks a ball, tick "Yes" for this item.)* 	☐	☐	☐
9 Does your child walk either up or down at least two steps by himself? You can look for this at a shop, in a playground, or at home. *(Tick "Yes" even if he holds onto the wall or handrail.)* 	☐	☐	☐

MOVEMENT SKILLS *Try each activity with your child* (continued)	YES	SOMETIMES	NOT YET
10 Does your child run fairly well, stopping himself without bumping into things or falling? 	☐	☐	☐
11 Does your child jump with both feet leaving the floor at the same time? 	☐	☐	☐
12 Without holding onto anything for support, does your child kick a ball by swinging his leg forward? 	☐	☐	☐
13 Does your child get a spoon into his mouth right side up so that the food usually doesn't spill?	☐	☐	☐
14 Does your child turn the pages of a book by himself? *(He may turn more than one page at a time.)*	☐	☐	☐
15 Does your child use a turning motion with his hand while trying to turn door knobs, wind up toys, twist tops, or screw lids on and off jars?	☐	☐	☐
16 Does your child turn switches off and on?	☐	☐	☐
17 Does your child stack seven small blocks or toys on top of each other by himself? *(You could also use cotton reels, small boxes, or toys that are about 1 inch in size.)*	☐	☐	☐
18 Does your child thread a shoelace through either a bead or an eyelet of a shoe? 	☐	☐	☐
PROBLEM SOLVING *Try each activity with your child*	**YES**	**SOMETIMES**	**NOT YET**
19 After he watches you draw a line from the top of the paper to the bottom with a crayon (or pencil or pen), does your child copy you by drawing a single line on the paper in any direction? *(Scribbling back and forth does not count as "yes.")* 	☐	☐	☐
20 Without showing him how, does your child purposefully turn a small, clear bottle upside down to tip out a crumb or sweet? *(You can use a fizzy-drink bottle or baby bottle.)*	☐	☐	☐
21 Does your child pretend objects are something else? For example, does your child hold a cup to his ear, pretending it is a telephone? Does he put a box on his head, pretending it is a hat? Does he use a block or small toy to stir food?	☐	☐	☐
22 Does your child put things away where they belong? For example, does he know his toys belong on the toy shelf, his blanket goes on his bed, and dishes go in the kitchen?	☐	☐	☐
23 If your child wants something he cannot reach, does he find a chair or box to stand on to reach it?	☐	☐	☐
24 While your child watches, line up four objects like blocks or cars in a row. Does he copy or imitate you and line up four objects in a row? *(You can also use cotton reels, small boxes, or other toys.)* 	☐	☐	☐

Appendix 4 continued



PERSONAL-SOCIAL *Try each activity with your child* — YES / SOMETIMES / NOT YET

25 Does your child drink from a cup or glass, putting it down again with little spilling?

26 Does your child copy activities you do, such as wipe up a spill, sweep, shave, or comb hair?

27 Does your child eat with a fork?

28 When playing with either a stuffed animal or doll, does your child pretend to rock it, feed it, change its nappies, put it to bed, and so forth?

29 Does your child push a little shopping trolley, push chair, or wagon, steering it around objects and backing out of corners if he cannot turn?

30 Does your child call himself "I" or "me" more often than his own name? For example, "I do it." more often than "John do it."

ABOUT YOUR CHILD'S HEALTH — YES / NO

31 Since your child came home from hospital after the birth has your doctor prescribed any medicine to be taken for more than two weeks? (Office use)

If yes, please give their names:

32 Over the last 3-6 months have you had to take your child to see your general practitioner for anything other than routine assessment?

If yes, how many times ☐☐ times

What for? *(please give details of each visit)*

33 Have you taken your child to a clinic to see a specialist since he first came home after the birth?

If yes, how many times ☐☐ times

What for? *(please give details of each visit)*

34 Has your child ever been admitted to hospital?

If yes, how many times ☐☐ times

What for? *(please give details of each admission)*

35 How tall is your child? ☐ feet ☐☐ inches OR ☐☐☐ cms

Date when your child was measured / /

36 How heavy is your child? ☐ stones ☐☐ pounds OR ☐☐ kilos ☐☐☐ gms

Date when your child was weighed / /

SOME GENERAL QUESTIONS ABOUT YOUR CHILD — YES / NO

37 Do you think your child hears well? (Office use)

If no, explain:

38 Do you think your child talks like other toddlers of the same age?

If no, explain

39 Can you understand most of what your child says?

If no, explain

Page 3

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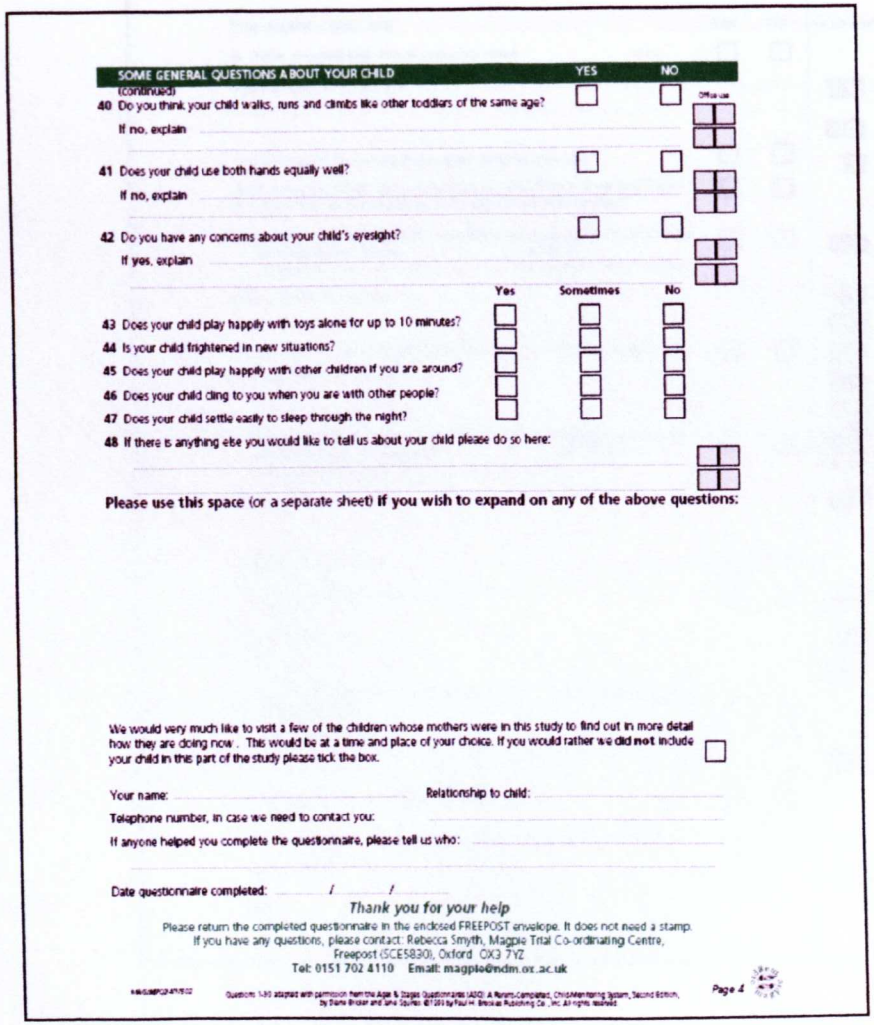

SOME GENERAL QUESTIONS ABOUT YOUR CHILD (continued) — YES / NO

40 Do you think your child walks, runs and climbs like other toddlers of the same age? (Office use)

If no, explain

41 Does your child use both hands equally well?

If no, explain

42 Do you have any concerns about your child's eyesight?

If yes, explain

	Yes	Sometimes	No
43 Does your child play happily with toys alone for up to 10 minutes?			
44 Is your child frightened in new situations?			
45 Does your child play happily with other children if you are around?			
46 Does your child cling to you when you are with other people?			
47 Does your child settle easily to sleep through the night?			

48 If there is anything else you would like to tell us about your child please do so here:

Please use this space (or a separate sheet) **if you wish to expand on any of the above questions:**

We would very much like to visit a few of the children whose mothers were in this study to find out in more detail how they are doing now. This would be at a time and place of your choice. If you would rather we did not include your child in this part of the study please tick the box. ☐

Your name: Relationship to child:

Telephone number, in case we need to contact you:

If anyone helped you complete the questionnaire, please tell us who:

Date questionnaire completed: / /

Thank you for your help

Please return the completed questionnaire in the enclosed FREEPOST envelope. It does not need a stamp.
If you have any questions, please contact: Rebecca Smyth, Magpie Trial Co-ordinating Centre,
Freepost (SCE5830), Oxford OX3 7YZ
Tel: 0151 702 4110 Email: magpie@ndm.ox.ac.uk

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Appendix 5

Woman's questionnaire

Please complete as soon as possible

We would like to hear about your health and wellbeing since was born. Please tick the most appropriate box for each question, giving further details where requested. If you need more space, write on the back of the questionnaire, referring to the question by number.

The information you give us will be confidential, and used only by the researchers.

Woman's name: **Child's name:**

If you would like to discuss any questions, please contact Rebecca Smyth (details at end of questionnaire), or ask your GP for advice.

Your health	**Yes**	**No**	For office use
1. Have you seen your GP about anything to do with your *own* health, since was born?	☐	☐	
If yes, approximately how many times have you seen your GP? ☐ times			
What for?			
2. Have you been to a hospital clinic to see a specialist about your *own* health, since was born?	☐	☐	
If yes, approximately how many times have you visited a hospital clinic? ☐ times			
What for?			
3. Have you been admitted to hospital, since going home after was born? *(do not include admissions due to another pregnancy)*	☐	☐	
If yes, how many times have you been admitted to hospital? ☐ times			
What for? *(please tell us about each admission)*			
4. Have you seen anyone else about your health, or how you feel, since going home after was born?	☐	☐	
If yes, who?			
What for?			
5. Before your pregnancy with , did you ever have high blood pressure?	☐	☐	
If yes, please tell us about it			
Was this *only* while you were taking the contraceptive pill?	☐	☐	

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Your health *(continued)*	**Yes**	**No**	For office use
6. Have you had high blood pressure since was born?	☐	☐	
If yes, please tell us about it			
Was this *only* while you were taking the contraceptive pill?	☐	☐	
Were you given advice about things you could do to help lower your blood pressure, such as losing weight, exercising or stopping smoking?	☐	☐	
7. Has your doctor said that you need to take any medicine/s for your blood pressure, since was born? *(do not include any medicine taken in the first six weeks after the birth)*	☐	☐	
If yes, please list them *all*			
8. Are you taking any medicine/s for your blood pressure *now*?	☐	☐	
If yes, please list them *all*			
9. Has your doctor said that you need to take any *other* medicine for more than two weeks, since was born? *(do not include any medicine for high blood pressure)*	☐	☐	
If yes, please list them *all*			
Further pregnancies	**Yes**	**No**	
10. Have you used any contraception since was born?	☐	☐	
If yes, which one/s			
11. Did having pre-eclampsia (toxaemia) contribute to your choice of contraceptive?	☐	☐	
If yes, please explain how			
12. Have you tried to get pregnant again since was born?	☐	☐	
If no, did having pre-eclampsia (toxaemia) contribute to your decision?	☐	☐	
Please explain			

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Appendix 5 continued

Further pregnancies *(continued)* | **Yes** | **No** | For office use

13. Have you been pregnant again since was born? ☐ ☐

If yes, how many more pregnancies have you had? ☐ number

how many of these were miscarriages? ☐ number

during how many did you have pre-eclampsia (toxaemia) or eclampsia? ☐ number

are you pregnant now? ☐ ☐

Please tell us about any children you have had in the last two years.....

.....

Your participation in the Magpie Trial

14. If time suddenly went backwards, and you had to do it all over again, would you agree to participate in the Magpie Trial?

☐ definitely yes ☐ probably yes ☐ probably no ☐ definitely no ☐ not sure

Please explain your answer.....

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15. Please tell us if there was anything about the Magpie Trial that you think could have been done better:

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.....

16. Please tell us if there was anything about the Magpie Trial, or your experience of joining the trial, that you think was particularly good:

.....

.....

.....

.....

.....

About you | **Yes** | **No** | For office use

17. Are you currently: married, or living with a long term partner ☐
single ☐
divorced or separated ☐
widowed ☐
other, please explain ..... ☐

18. What is your usual occupation? .....

19. If you are married or have a long term partner, what is their usual occupation?

.....

20. How old were you when you left full time education? ☐ years

21. What is your highest educational qualification? .....

22. Has your mother, your sister/s, or any other relative on your mother's side of the family ever had pre-eclampsia (toxaemia) or eclampsia? ☐ ☐

If yes, what is their relationship to you? .....

Please write here about anything else you would like to tell us, continue on a separate sheet if necessary.

Date completed: ___/___/___ ***Thank you for your help***

We would like to visit a few of the women and children to find out in more detail how they are doing now. If you were selected for a visit, we would contact you to arrange a time and place convenient for you. If you would rather we did *not* include you in this part of the study, please tick here. ☐

Please return the completed questionnaire in the enclosed envelope it does not need a stamp

If you have any questions, please contact the study midwife, Rebecca Smyth by telephone (0151 702 4110), by email (magpie@ndm.ox.ac.uk) or by post.

Letters addressed to her at the Magpie Trial Co-ordinating Centre, FREEPOST, Institute of Health Sciences, Oxford OX3 7YZ, do not need a stamp.

Appendix 6

Results of the Magpie Trial

Thank you

You were one of over 10,000 women who agreed to take part in the Magpie Trial. The short term results of this study were published recently in a medical journal called *The Lancet*, and were publicised quite widely in the media.

Many women who contribute to research would like to know the outcome of the study. This leaflet reminds you of what the study was about, summarises the findings, and tells you how you can find out more, if you want to.

Magnesium sulphate halves the risk of convulsions for women with pre-eclampsia....

... that was the main finding of this massive scientific trial. It also showed that magnesium sulphate is a safe treatment for mothers and their unborn babies.

What is pre-eclampsia?

Pre-eclampsia (formerly known as 'toxaemia') is a complication of pregnancy marked by raised blood pressure, the appearance of protein in the urine and (often) swelling of the hands, feet and face.

Although the condition is normally mild, some women develop a severe form, which can give rise to problems in the brain, kidneys, liver, lungs, heart or blood clotting system. Since pre-eclampsia has its origins in the placenta – the organ that joins mother and baby – it can affect the unborn baby too, causing growth restriction and oxygen deficiency in bad cases.

Although pre-eclampsia is fairly common and potentially serious, it is poorly understood by scientists and doctors. This makes it difficult to treat and, so far, impossible to prevent.

What is eclampsia?

One of the most serious complications of pre-eclampsia is eclampsia, when the mother suffers convulsions that can be dangerous for her and her unborn baby.

Eclampsia is quite rare in developed countries like the UK, where it effects about one pregnant woman in every 2,000. But it is much commoner in developing areas of the world like India, Pakistan and much of Africa, where it is a major killer of mothers and babies.

The first big breakthrough in the treatment of eclampsia came in 1995, when a forerunner of the Magpie Trial established that doctors could prevent recurrent fits in women with eclampsia by injecting them with magnesium sulphate. This trial also showed that magnesium sulphate was better than two other 'anticonvulsant' drugs, diazepam (Valium) and phenytoin, at stopping the fits.

About the Magpie Trial

The Magpie Trial (**Ma**gnesium Sulphate for Preventing Eclampsia), involved many of the same doctors and midwives from the same countries as the last one. The co-ordinators of both studies, based in Oxford, wanted to go one step further and establish whether magnesium sulphate could actually prevent eclampsia.

In fact, magnesium sulphate had already been used for many years for this purpose in some countries, particularly the United States. But the doctors there had no reliable scientific evidence that it actually worked; neither could they say for sure that the treatment was harmless for mothers and their unborn babies.

In the Magpie Trial women with pre-eclampsia were randomly assigned to treatment with either magnesium sulphate or an inactive treatment (placebo), given in hospital, by injection, over a period of 24 hours. The trial was 'double blind' in that neither the women nor their doctors were aware of whether they were receiving the active treatment or placebo. Trials designed like this are seen as the best way to achieve reliable, unbiased results.

The trial had been expected to last until the end of March 2002. But it was stopped ahead of schedule in November 2001, when it became clear that the researchers had already proved beyond reasonable doubt that the treatment worked.

What the trial showed

The main findings of the trial were as follows:

- Only 40 women treated with magnesium sulphate developed eclampsia, compared with 96 on placebo. This represents a substantial risk reduction of 58%
- There were fewer maternal deaths in the magnesium sulphate group - 11, compared with 20 in the placebo group. But because of the very small overall number of deaths, it is possible that chance played a role in some of the apparent difference between the groups
- Magnesium sulphate, as prescribed in the trial, is safe for both mothers and babies, although unpleasant maternal side effects, particularly flushing, were common
- Magnesium sulphate was linked with a 30% reduction in the risk of placental abruption - a premature separation of the placenta from the womb

In a paper published in *The Lancet*, the Magpie research team concluded:

> *'Magnesium sulphate reduces the risk of eclampsia, and it is likely that it also reduces the risk of maternal death. At the dosage used in this trial it does not have any substantive harmful effects on the mother or child, although a quarter of women will have side effects.'*

They will now move on to the final follow up phase of the study (see below).

What this means for women

It is now likely that treatment with magnesium sulphate will be made available in the UK to women with pre-eclampsia who are considered at risk of eclampsia. This treatment must be given in hospital, because mothers and babies need to be monitored carefully for the duration.

A word of warning

It is important to understand that this is not a self-help treatment and there is no suggestion that women can prevent either eclampsia or pre-eclampsia by taking magnesium supplements in pregnancy. The treatment tested in this trial must be prescribed by a doctor and given by injection in a hospital setting.

The Magpie Trial Follow up Study

This ongoing part of the study involves following up a proportion of babies born to mothers in the trial to rule out the possibility of any harmful long-term effects of exposure to magnesium sulphate treatment in the womb. Women are being asked to complete a questionnaire about themselves and their children, and some are also being visited to find out in more detail how they are doing.

How to get further Information

To read The Lancet paper

- order it from your local library, using this reference (The Magpie Trial Collaborative Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet* 2002; 359: 1877-90)
- read it on the Lancet website at www.thelancet.com
- download the pdf file free of charge from the Magpie Trial website at www.magpietrial.org.uk

To find out more about the Magpie Trial Follow up Study

- look at the Magpie Trial website at www.magpietrial.org.uk
- contact the Co-ordinating Centre, at the address below

To find out more about pre-eclampsia or eclampsia

For general information about pre-eclampsia or eclampsia, contact the charity:

Action on Pre-eclampsia (APEC)
84-88 Pinner Road, Harrow
Middlesex, HA1 4HZ

email: info@apec.org.uk
website: www.apec.org.uk
Helpline: 020 8427 4217

Magpie Trial Co-ordinating Centre
Institute of Health Sciences, Headington, Oxford OX3 7LF
Tel: 01865 226642, Email: magpie@ndm.ox.ac.uk

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Appendix 7

Search Strategy (1)

Database: Ovid MEDLINE(R) 1966 to June Week 2 2006

#	Search terms	Number of retrievals
1	exp Comprehension/	1281
2	understand$.mp.	195531
3	(knowledge or perception$).mp.	200530
4	(experience or experiences).mp	251036
5	attitude$.mp	141103
6	(view$ or perspective$ or opinion$).ti,ab.	250472
7	reaction$.ti,ab.	431659
8	exp communication/	189698
9	exp. ethics/	932277
10	exp informed consent/	23763
11	exp Parents/px [Psychological]	13968
12	professional-family relations/	6747
13	physician-patient relations/	37193
14	patient participation/	9184
15	exp Randomized Controlled Trials/	32564
16	rct$.ti,ab.	2356
17	randomis$.ti,ab.	22932
18	randomz$.ti,ab.	122847
19	exp Questionnaires/	111004
20	question$.ti,ab.	232668
21	interview$.ti,ab.	87478
22	exp Interviews/	15416
23	qualitative.af.	45320
24	exp qualitative research/	1332
25	or/1-7	1307212
26	or/8-14	329763
27	or/15-18	163956
28	or/19-24	394765
29	25 and 27 and 28	3302
30	26 and 27	3506
31	29 or 30	6363
32	limit 31 to human	6185

Appendix 7 continued

Search Strategy (2)

Database: Ovid MEDLINE(R) 1966 to June Week 3 2006

#	Search terms	Number of retrievals
1	exp randomized controlled trials/	40395
2	participa$.mp.	258585
3	exp Informed Consent/	25451
4	(woman or women).mp	422109
5	1 and 2 and 3 and 4	5
6	(pregnancy or pregnant or mother$).mp.	586854
7	1 and 2 and 3 and 6	8
8	(attitude$ or knowledge or perception$ or experience$ or understand$ or view$ or opinion$ or perspective$).mp.	1168595
9	1 and 2 and 8 and (4 or 6)	138
10	px.fs.	409929
11	1 and 2 and 10 and (4 or 6)	67
12	5 or 7 or 9 or 11	165
13	1 and (4 or 6) and 8	668
14	1 and (4 or 6) and 10	197
15	13 or 14	768
16	15 not 12	607
17	*"patient selection"/	6443
18	patient selection.mp	28995
19	female.mp.	4368576
20	4 or 6 or 19	4408262
21	18 and 20	11636
22	8 or 10	1429700
23	21 and 22	3347
24	1 and 23	150
25	18 and 6	1203
26	1 and 25	35
27	(recruit$ or enrol$).mp	128113
28	17 or 27	133702
29	1 and 3 and 4 and 28	3
30	1 and 3 and 6 and 28	4
31	1 and 8 and (4 or 6) and 28	99
32	1 and 28 and 10 and (4 or 6)	37
33	qualitative study.mp.	3651
34	1 and 28 and (10 or 33)	179
35	interview$.mp.	114461
36	1 and 28 and 10 and (34 or 35)	177

Appendix 7 continued

Search Strategy (3)

Database: CINAHL 1982 to June Week 3 2006

#	Search terms	Number of retrievals
1	exp randomized controlled trials/	34390
2	participa$.mp.	58411
3	exp Informed Consent/	4913
4	(woman or women).mp	55444
5	1 and 2 and 3 and 4	6
6	(pregnancy or pregnant or mother$).mp.	51679
7	1 and 2 and 3 and 6	2
8	(attitude$ or knowledge or perception$ or experience$ or understand$ or view$ or opinion$ or perspective$).mp.	186440
9	1 and 2 and 8 and (4 or 6)	274
10	px.fs.	0
11	1 and 2 and 10 and (4 or 6)	0
12	5 or 7 or 9 or 11	277
13	1 and (4 or 6) and 8	821
14	1 and (4 or 6) and 10	0
15	13 or 14	821
16	15 not 12	547
17	*"patient selection"/	574
18	patient selection.mp	3506
19	female.mp.	248650
20	4 or 6 or 19	260868
21	18 and 20	835
22	8 or 10	186440
23	21 and 22	188
24	1 and 23	18
25	18 and 6	79
26	1 and 25	9
27	(recruit$ or enrol$).mp	24756
28	17 or 27	25284
29	1 and 3 and 4 and 28	5
30	1 and 3 and 6 and 28	2
31	1 and 8 and (4 or 6) and 28	154
32	1 and 28 and 10 and (4 or 6)	0
33	qualitative study.mp.	3348

Appendix 8

Your participation in the Magpie Trial

14. If time suddenly went backwards, and you had to do it all over again, would you agree to participate in the Magpie Trial?

☐ definitely yes ☐ probably yes ☐ probably no ☐ definitely no ☐ not sure

Please explain your answer.....

.....

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.....

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15. Please tell us if there was anything about the Magpie Trial that you think could have been done better:

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16. Please tell us if there was anything about the Magpie Trial, or your experience of joining the trial, that you think was particularly good:

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Appendix 9

The QUOTE Study interview schedule

Before the interview starts

Thank the woman for taking the time to be interviewed

Give opportunity for the woman to read the study information leaflet again

Recap for her the purpose of the study (example of text below):

"I would like to find out about your experiences of joining the Magpie Trial. Especially what it felt like when you made your decision to join. I am interested in finding out if you have any thoughts about the way it was carried out and about the trial since. We hope that understanding more about women's experiences of research will help us improve trials in the future".

Introduction by RS:

I will explain to the woman that although I am part of the Magpie Trial team I don't want her to feel hindered in what she has to say. That I'm talking with her because it's important to know exactly what her experience of Magpie was. I will tell her I won't take any comments personally whatever she says, good or bad, just here to listen and make sure I've understood her point of view. Everything se says during the interview will be strictly confidential and only shared with members of this study team. Comments made will not be reported back to the hospital that she was recruited at or any clinician involved in the care & she will not be able to be identified in any final report. I will encourage the woman to be as truthful as possible regarding her experiences of joining the Magpie Trial.

Introduction by LW:

Explain to the woman that you are not a member of the Magpie Trial team, & that you work as research midwife at the Liverpool Women's Hospital. That you have been asked to carry out some of the interviews because you are not part of the trial and it is important that the women feel able to say exactly what they think about the trial. That you're here because it's important for the research team to know exactly what their experience of Magpie was. Tell

them you will not take any comments personally whatever they say, good or bad, just that you are here to listen and make sure you've understood their view so that the Magpie Trial team get their point of view. Explain that everything they say during the interview will be strictly confidential and only shared with members of this study team. Comments made will not be reported back to the hospital that they were recruited at or any clinician involved in their care & they will not be able to be identified in any final report. Encourage the woman to be as truthful as possible regarding her experiences of joining the Magpie Trial.

The Interview

Introduction

Remind the woman that interview usually takes between one & two hours And that if she wants she can be stop the interview at any time without giving a reason. Also that she does not need to answer any questions that she doesn't want to. Ask her if she has any questions to ask prior to proceeding, if LW cannot answer them she will pass any queries on to RS & either proceed with the interview or defer it for the time being.
Obtain written consent to tape-record interview

Schedule

The schedule outlined below will not be used verbatim, but is a guide as to the areas that will be talked about with the women. The aim is to cover most if not all of the questions, but this will very much depend on the individual woman. Some women may not want to talk about a particular issue that is on the schedule and this is fine, also she should be allowed to decline answering a question if she wants. Alternatively some women may want to talk about an issue that is not part of the schedule. These may be important to the woman therefore give her time to reflect on her own experiences & what is important to her. It is important though not to allow the interview to deviate too much into unrelated areas.

It is important to recognise that the interview may bring up difficult or unhappy memories for the women. The interviewer will give the woman the opportunity

to talk about these situations. She may be some unresolved questions about either the trial, pre-eclampsia or the care received at the hospital. Regarding questions related to the Magpie Trial they should be directed to RS. Regarding pre-eclampsia; questions can be answered at the time of the interview, as both interviewers are midwives, additional information and support can be provided by the support group (Action against Pre-Eclampsia). Regarding care the woman received in hospital, it may be appropriate for the woman to contact her consultant to explain these unresolved issues. The interviewer will need to use her own judgement as to how to deal with each situation.

The Magpie Trial results will be published in the Lancet on 1st June 2002 and there will probably be some coverage by the media. So it could be possible that some of the women interviewed will know them. Also if they want to know their treatment allocation they can contact (in writing) the Magpie centre and they will be told.

Section 1

Questions to set the scene:

I'll begin by asking you to describe the situation when you were asked to join the Magpie Trial, for example:

When was pre-eclampsia diagnosed?

What happened?

Had you previously had problems with your blood pressure?

How long had you been in hospital?

Where you recruited to Magpie antenatally or postnatally?

Where you in labour?

Who was with you at the time?

Section 2

Describing the process of recruitment:

Now I would like to ask you about your experience of when you were asked to join the trial:

Do you remember being asked to join the trial?

Describe the process?

How did being invited to join the trial make you feel?

Who talked to you about the trial?

When were you asked to join the trial, what do you think about the timing?

Can you remember what you were told about the trial?

Were you given trial information leaflet to read? (show one if needed)

What did you think of the leaflet?

Did you ask any questions?

Was your partner/family involved in deciding whether you should join?

Can you describe to me the feelings you had once you'd agreed to join?

Did you think there were any benefits or advantages to you or your baby by being in the trial?

Did you think there were any risks or disadvantages to you or your baby by being in the trial?

Did you at the time have any anxieties about joining?

Why did you join the trial?

Was there any follow up after joining the trial whilst still in hospital?

Section 3

What woman understood of the Magpie Trial:

I am interested in finding out your opinion about how and why the trial was carried out:

Can you tell me what you understand about the following & how do they make you feel? (If woman doesn't understand theses concepts explain them to her then ask her how does it make her feel?)

The study

Randomisation

Uncertainty/equipoise

Placebo control

Double blinding

Section 4

Since recruitment:

In between the time that you were discharged from hospital and when we contacted you again, did you ever think about the trial?

Thoughts since?

Unresolved questions?

Was there anything you think could have improved this experience?

Was there any aspect of the Magpie Trial or care generally that they would have liked more information about?

Do you have any anxieties now about joining?

More or less likely to take part in research?

Thoughts about the results of Magpie Trial?

Thoughts about researchers giving participants trial results?

Thoughts about the Follow up study?

Section 5

Views on research generally:

Finally I would like to ask you do you have any general thoughts/comments you would like to make either about the Magpie Trial and the way it was done or research generally?

Anything about the way midwives/doctors go about asking people to help with research?

Information given?

Making joining easier?

Section 6

Conclusion:

That is all of the questions but is there anything else that you would like to add about your experience of joining the Magpie Trial? or ask me?

At the end of the interview ask the woman if she would like to know the results of this study: YES/NO

Appendix 10 Characteristics of women interviewed

Characteristics of women										
Women (n=1-10)	**01**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**
At trial entry										
Age at recruitment	37	25	29	32	26	23	38	39	34	36
Pregnant at the time of being recruited	yes	no	yes	yes	yes	yes	yes	yes	yes	yes
Multiple pregnancy	no	no	no	no	no	no	no	no	no	no
Primiparous	no	yes	yes	yes	yes	yes	yes	yes	no	yes
Severe pre-eclampsia*	yes	no	yes	no	yes	yes	yes	no	yes	yes
Relating to Magpie Trial										
Randomised magnesium sulphate	yes	no	no	yes	no	no	yes	no	yes	no
Woman thinks she had magnesium sulphate	yes	no idea	yes	yes	yes	no idea	yes	no idea	no	no
Side effects caused by the trial treatment	no	no	no	yes	no	no	no	no	no	no
More than 24 hours on trial treatment	yes	no	no	yes	no	no	yes	no	yes	no
Outcome after randomisation (women)**										
Delivered by caesarean section	yes	yes	yes	yes	yes	no	no	no	yes	yes
Nursed in intensive care unit / high dependency unit	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Outcome infant										
Child born prematurely (less than 34 weeks)	yes	yes	yes	yes	yes	no	no	no	no	yes
Child admitted to neonatal intensive care unit	yes	yes	yes	yes	yes	no	no	no	no	yes
Child still in hospital 6 weeks after birth	yes	no	yes	no	no	no	no	no	no	yes
Since going home										
Could recall receiving written results / media coverage	yes	yes	yes	no	yes	yes	yes	yes	yes	yes
Requested unblinding	no	no	no	no	no	no	no	no	no	no
Child screening 'screen positive' on the ASQ	yes	yes	yes	no	yes	yes	no	yes	yes	yes
Child with moderate or severe disability confirmed	no	no	no	no	no	no	no	no	no	yes
Serious long-term maternal morbidity***	no	yes	no	no	no	no	no	no	no	no
Had a home visit	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Responses to postal questionnaire										
Would join the trial again: Definitely yes	✓				✓	✓		✓		
Probably yes			✓				✓		✓	
Not sure		✓								
Probably no				✓						✓
Definitely no										
Not answered										

* diastolic blood pressure ≥100mmHg on 2 occasions or systolic blood pressure ≥170mmHg on 2 occasions and proteinurea ≥3+

**no woman had an eclamptic fit

***renal problems, stroke, severe hypertension, any chronic illness since birth of baby

Characteristics of women	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Women (n=11-20)										
At trial entry										
Age at recruitment	27	30	23	36	19	30	36	28	29	27
Pregnant at the time of being recruited	no	yes	yes	yes	yes	yes	no	yes	no	no
Multiple pregnancy	no	no	no	no	no	no	no	no	no	no
Primiparous	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Severe pre-eclampsia*	no	no	yes	yes	no	yes	no	yes	yes	yes
Relating to Magpie Trial										
Randomised magnesium sulphate	no	no	yes	yes	no	yes	no	no	yes	yes
Woman thinks she had magnesium sulphate	no idea	yes	yes	no idea	yes	yes	no	no	yes	yes
Side effects caused by the trial treatment	no	yes	no	no	no	yes	no	no	no	yes
More than 24 hours on trial treatment	no	yes	yes	no	yes	no	yes	yes	yes	no
Outcome after randomisation (women)**										
Delivered by caesarean section	yes	no	no	no	no	no	no	yes	yes	yes
Nursed in intensive care unit / high dependency unit	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Outcome infant										
Child born prematurely (less than 34 weeks)	no	no	no	no	no	no	no	no	yes	no
Child admitted to neonatal intensive care unit	no	no	no	no	no	yes	no	yes	yes	no
Child still in hospital 6 weeks after birth	no	no	no	no	no	no	no	no	no	no
Since going home										
Could recall receiving written results / media coverage	yes	yes	yes	yes	yes	no	no	yes	yes	yes
Requested unblinding	no	no	yes	no	no	no	yes	no	no	no
Child screening 'screen positive' on the ASQ	no	no	no	yes	no	yes	yes	yes	no	yes
Child with moderate or severe disability confirmed	no	no	no	no	no	no	no	no	no	no
Serious long-term maternal morbidity***	no	no	no	no	no	no	no	no	no	no
Had a home visit	yes	no	no	yes	no	yes	yes	yes	yes	yes
Responses to postal questionnaire										
Would join the trial again: Definitely yes	✓	✓	✓	✓		✓		✓	✓	
Probably yes							✓			
Not sure										
Probably no					✓					
Definitely no										
Not answered										✓

Appendix 10 Characteristics of women interviewed (continued)

Characteristics of women										
Women (n=21-30)	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**
At trial entry										
Age at recruitment	16	21	31	37	29	34	33	38	20	17
Pregnant at the time of being recruited	yes	yes	no	yes	yes	no	yes	no	yes	yes
Multiple pregnancy	no	yes	no	no	no	no	no	no	no	no
Primiparous	yes	no	yes	yes	yes	yes	no	no	yes	yes
Severe pre-eclampsia*	no	no	no	yes	yes	yes	no	yes	yes	yes
Relating to Magpie Trial										
Randomised magnesium sulphate	yes	no	yes	yes	yes	yes	no	yes	no	yes
Woman thinks she had magnesium sulphate	yes	no idea	yes	yes	no idea	no idea	no	no	no	yes
Side effects caused by the trial treatment	yes	no	yes	yes	no	no	no	no	no	yes
More than 24 hours on trial treatment	yes	yes	yes	yes	yes	yes	no	yes	yes	no
Outcome after randomisation (women)**										
Requested unblinding	no	no	no	no	no	no	no	no	no	no
Delivered by caesarean section	no	no	yes	yes	yes	yes	no	yes	no	no
Nursed in intensive care unit / high dependency unit	no	yes	yes	yes	yes	yes	yes	yes	yes	yes
Outcome infant										
Child born prematurely (less than 34 weeks)	yes	no	no	no	yes	yes	no	yes	no	no
Child admitted to neonatal intensive care unit	yes	no	no	yes	yes	yes	no	yes	no	no
Child still in hospital 6 weeks after birth	no	no	no	no	no	yes	no	no	no	no
Since going home										
Could recall receiving written results / media coverage	yes	yes	yes	yes	yes	no	yes	yes	yes	yes
Requested unblinding	no	no	no	no	no	no	no	no	no	no
Child screening 'screen positive' on the ASQ	no	yes	no	yes	yes	No	no	yes	yes	no
Child with moderate or severe disability confirmed	no	no	no	no	no	yes	no	yes	no	no
Serious long-term maternal morbidity***	no	no	no	no	yes	no	yes	yes	no	no
Had a home visit	no	yes	yes	yes	yes	yes	yes	no	yes	yes
Responses to postal questionnaire										
Would join the trial again: Definitely yes		✓	✓	✓	✓					
Probably yes						✓	✓	✓		✓
Not sure	✓									
Probably no										
Definitely no										
Not answered									✓	

Appendix 10 Characteristics of women interviewed (continued)

Characteristics of women	31	32	33	34	35	36	37	38	39	40
Women (n=31-40)										
At trial entry										
Age at recruitment	26	20	26	32	31	35	36	33	25	23
Pregnant at the time of being recruited	yes	yes	yes	no	yes	yes	no	yes	yes	yes
Multiple pregnancy	yes	no	no	yes	no	no	yes	no	no	no
Primiparous	yes	yes	yes	no	no	yes	no	yes	no	yes
Severe pre-eclampsia*	yes	yes	no	no	yes	no	yes	no	yes	no
Relating to Magpie Trial										
Randomised magnesium sulphate	yes	no	yes	yes	yes	no	yes	no	yes	no
Woman thinks she had magnesium sulphate	yes	no idea	yes	yes	yes	no idea	yes	yes	no	no idea
Side effects caused by the trial treatment	yes	no	no	yes	no	no	no	no	no	no
More than 24 hours on trial treatment	yes	no	yes	yes	no	no	yes	yes	yes	no
Outcome after randomisation (women)**										
Delivered by caesarean section	yes	yes	no	yes	no	yes	yes	no	yes	no
Nursed in intensive care unit / high dependency unit	yes	yes	yes	yes	no	yes	yes	no	yes	no
Outcome infant										
Child born prematurely (less than 34 weeks)	no	yes	no	no	no	no	no	no	no	no
Child admitted to neonatal intensive care unit	yes	yes	no	no	no	no	no	no	no	no
Child still in hospital 6 weeks after birth	no	yes	no	no	no	no	no	no	no	no
Since going home										
Could recall receiving written results / media coverage	no	yes	yes	yes	yes	yes	yes	yes	yes	no
Requested unblinding	yes	no	no	no	no	no	no	no	no	no
Child screening 'screen positive' on the ASQ	yes	no	no	yes	no	no	no	yes	yes	no
Child with moderate or severe disability confirmed	no	no	no	no	no	no	no	no	no	no
Serious long-term maternal morbidity***	no	no	no	no	no	no	no	no	no	no
Had a home visit	yes	no	yes	yes	no	no	no	yes	yes	no
Responses to postal questionnaire										
Would join the trial again: Definitely yes	✓		✓		✓	✓	✓			
Probably yes								✓	✓	
Not sure		✓								
Probably no				✓						✓
Definitely no										
Not answered										

Appendix 11

QUOTE Study Information Leaflet

Magpie Trial letterhead
Women's Information Leaflet
Qualitative Understanding of Trial Experience

Thank you for reading this letter. You are being invited to take part in a research study. Before you decide it is important for you to understand why we are doing the research and what it will involve. Please take time to read the following information carefully and discuss it with others if you want. Ask us if there is anything that is not clear or if you would like more information.

Purpose of the Study
We would like to find out about different women's experiences of joining the Magpie Trial. We are especially interested in knowing what it felt like when you made the decision to join and your understanding of the trial. We are interested in finding out if you have had any thoughts about the way it was carried out and about the trial since. We hope that understanding more about women's experiences of research will help us improve trials in the future and make them more relevant to women and their families.

Work carried out during this study will also be part of a postgraduate degree by Rebecca Smyth at Liverpool University. Rebecca Smyth works as a Research Midwife for the Magpie Trial and its Follow up Study.

What will happen to me if I take part?
If you are interested in taking part we will arrange for Rebecca Smyth or another researcher to meet with you at a time and place convenient for you. The meeting usually takes between one and two hours. We would also like your permission to tape the interview. The reason for this is it is difficult to make notes and listen to you at the same time. During the interview we would be interested to hear about your experiences when you were invited to join the Magpie Trial, how you feel about the trial and your decision to join and what the experience has been like for you and your family.

It is completely your decision whether or not to take part in this study. If you would like to take part please sign the consent form and return it in the freepost envelope provided, no stamp required. If you decide to take part you are still free to withdraw at any time and without giving a reason.

What are the possible risks or benefits of taking part?
There are no risks, but some women in other similar studies have found talking about their own experiences of joining a trial helpful.

Will my taking part in this study be kept confidential?

Everything that you say during the interview will be strictly confidential. Once some notes from the tape have been made it will be destroyed. The notes will not contain your name or any other information which may identify you. Only the researchers involved in the study will have access to these notes.

What will happen to the results of the study?
The results are likely to be known in 2004 and we hope they will be published in various journals. It will not be possible to identify any individual person in any report of these results. At the end of the interview you will be asked if you would like to know the results of this study.

Who is organising and funding the study?
This study is funded by the Medical Research Council, as is the Magpie Trial.

Who has reviewed the study?
The study has been reviewed by the North West Research Ethics Committee.

Contact for further information
If you have any questions about taking part in the study do get in touch with Rebecca Smyth by letter or phone. She is based at the Liverpool Women's Hospital, University of Liverpool, Crown Street, Liverpool, L8 7SS. Tel 0151 702 4110

Thank you again for taking the time to read this letter.

Yours sincerely

Rebecca Smyth
Research Midwife
Liverpool Women's Hospital
University

Ann Jacoby
Professor
Liverpool University

Diana Elbourne
Professor
London

Appendix 12

QUOTE Study Consent Form

Magpie Trial letterhead
Women's Consent Form

Title of Project: QUOTE Study (Qualitative Understanding of Trial Experience)

Name of Researcher: Rebecca Smyth, Research Midwife

Please initial box

1. I confirm that I have read and understood the information sheet dated ..... (version .....) for the above study and have had the opportunity to ask questions ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected ☐

3. I agree to take part in the above study ☐

Name of participant	Date	Signature
Name of person taking consent (if different from researcher)	Date	Signature

Rebecca Smyth
Liverpool Women's Hospital
University of Liverpool
Obstetric and Gynaecology Dept
Crown Street
Liverpool
L8 7SS
0151 702 4110

Researcher	Date	Signature

1 copy for participant, 1 copy for researcher

Appendix 13

Invite to Study (*no home visit performed*)

Magpie Trial Letterhead
Contact details for RS
Invite letter

[Date]

[Woman's name]
[Address]

Dear [Woman's name]

Thank you for completing the Magpie Trial questionnaires. I am a research midwife working on the Magpie Trial Follow up Study. I would like to ask you whether you would be willing to meet me and talk with me or another researcher. We would like to hear more about your views of the Magpie Trial. We would be happy to meet at a time and place that is convenient to you.

Finding out more about the views and experiences of people like yourself will help others do better research in the future. The meeting usually takes between one and two hours. Everything you say will be in complete confidence.

I have enclosed an information leaflet which tells you a little more about the study and what it would mean for you. I hope it answers all your questions, but if not please contact me on my telephone number above. Leave a message on the answer machine if nobody answers, and I'll get back to you. It is for you to decide whether or not you take part. If you do decide to take part please sign the consent form enclosed and return it to me in the free post envelope, no stamp is required.

Thank you once again for your time and help. Your involvement in the Magpie Trial has helped enormously in trying to find out the best way to treat women with pre-eclampsia. We are very grateful to you

Kind regards

Rebecca Smyth
Research Midwife

Appendix 14

Thank you letter

Magpie Trial letterhead
Contact details for RS
QUOTE Study

Date

Woman's name & address

Dear (woman's name)

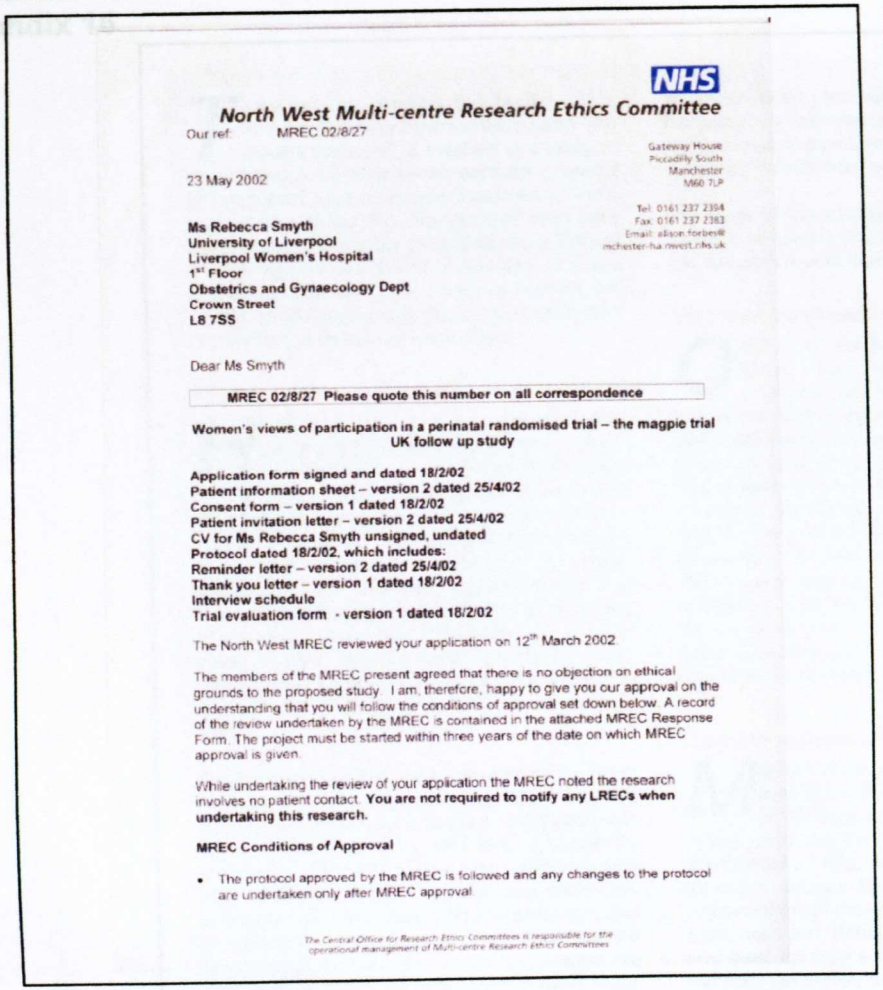
Thank you very much for being interviewed by [me/name of other researcher] regarding your involvement in the Magpie Trial. What you had to say was very interesting and has been really helpful in finding out about the views of women involved in the trial. I haven't yet analysed all the interviews, but when I do I will send you a summary of the results from the study.

May I take this opportunity to thank you also for initially joining the Magpie Trial and its Follow up Study. Your involvement in both has helped enormously in trying to find out the best way to treat women with pre-eclampsia. We are very grateful to you.

With best wishes for the future

Rebecca Smyth
Research Midwife

Appendix 15



NHS

North West Multi-centre Research Ethics Committee

Our ref: MREC 02/8/27

Gateway House
Piccadilly South
Manchester
M60 7LP

Tel: 0161 237 2394
Fax: 0161 237 2383
Email: alison.forbes@
mchester-ha.nwest.nhs.uk

23 May 2002

Ms Rebecca Smyth
University of Liverpool
Liverpool Women's Hospital
1st Floor
Obstetrics and Gynaecology Dept
Crown Street
L8 7SS

Dear Ms Smyth

MREC 02/8/27 Please quote this number on all correspondence

Women's views of participation in a perinatal randomised trial – the magpie trial UK follow up study

Application form signed and dated 18/2/02
Patient information sheet – version 2 dated 25/4/02
Consent form – version 1 dated 18/2/02
Patient invitation letter – version 2 dated 25/4/02
CV for Ms Rebecca Smyth unsigned, undated
Protocol dated 18/2/02, which includes:
Reminder letter – version 2 dated 25/4/02
Thank you letter – version 1 dated 18/2/02
Interview schedule
Trial evaluation form - version 1 dated 18/2/02

The North West MREC reviewed your application on 12th March 2002.

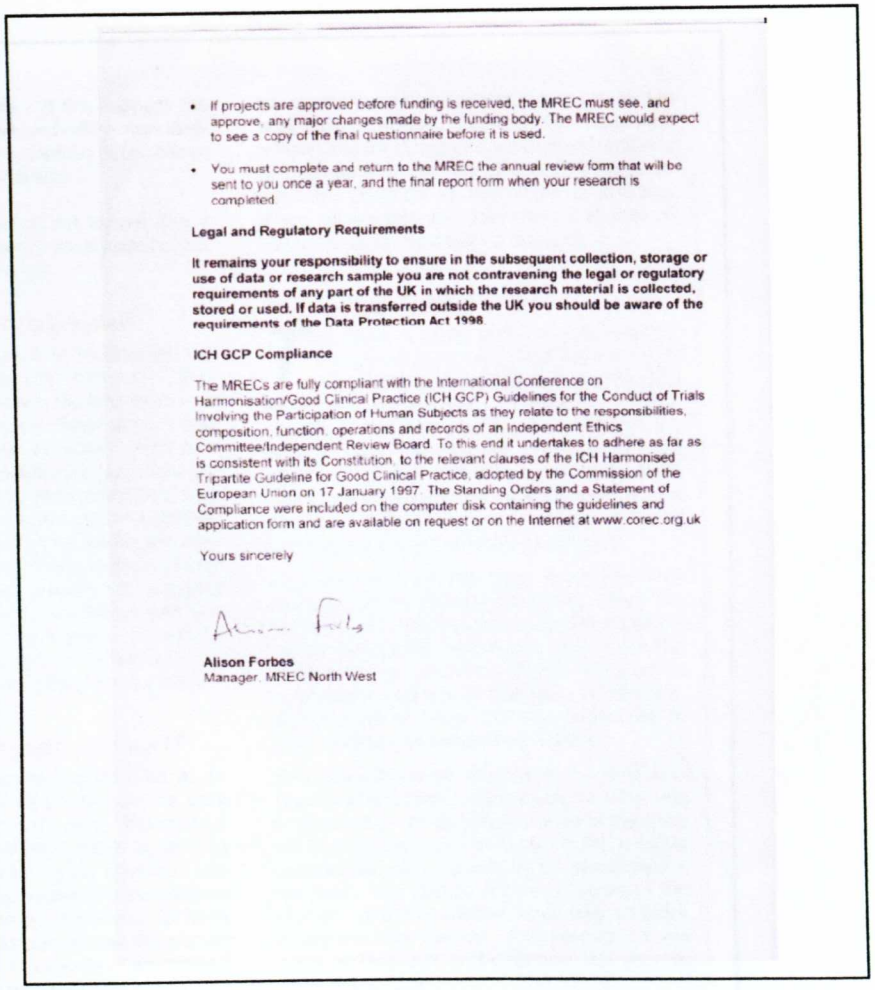
The members of the MREC present agreed that there is no objection on ethical grounds to the proposed study. I am, therefore, happy to give you our approval on the understanding that you will follow the conditions of approval set down below. A record of the review undertaken by the MREC is contained in the attached MREC Response Form. The project must be started within three years of the date on which MREC approval is given.

While undertaking the review of your application the MREC noted the research involves no patient contact. **You are not required to notify any LRECs when undertaking this research.**

MREC Conditions of Approval

- The protocol approved by the MREC is followed and any changes to the protocol are undertaken only after MREC approval.

The Central Office for Research Ethics Committees is responsible for the operational management of Multi-centre Research Ethics Committees



- If projects are approved before funding is received, the MREC must see, and approve, any major changes made by the funding body. The MREC would expect to see a copy of the final questionnaire before it is used.

- You must complete and return to the MREC the annual review form that will be sent to you once a year, and the final report form when your research is completed.

Legal and Regulatory Requirements

It remains your responsibility to ensure in the subsequent collection, storage or use of data or research sample you are not contravening the legal or regulatory requirements of any part of the UK in which the research material is collected, stored or used. If data is transferred outside the UK you should be aware of the requirements of the Data Protection Act 1998.

ICH GCP Compliance

The MRECs are fully compliant with the International Conference on Harmonisation/Good Clinical Practice (ICH GCP) Guidelines for the Conduct of Trials Involving the Participation of Human Subjects as they relate to the responsibilities, composition, function, operations and records of an Independent Ethics Committee/Independent Review Board. To this end it undertakes to adhere as far as is consistent with its Constitution, to the relevant clauses of the ICH Harmonised Tripartite Guideline for Good Clinical Practice, adopted by the Commission of the European Union on 17 January 1997. The Standing Orders and a Statement of Compliance were included on the computer disk containing the guidelines and application form and are available on request or on the Internet at www.corec.org.uk

Yours sincerely

Alison Forbes
Manager, MREC North West

Appendix 16

Thank you for reading this leaflet. This hospital, like many others in this country and around the world, is involved in a study to try and find out if magnesium sulphate is helpful for women with pre-eclampsia ('toxaemia'). This is an invitation to women, like yourself, who have pre-eclampsia to consider joining the study. If there is anything here you do not understand, or if you have other questions, your doctor or midwife will be able to discuss this with you or you can contact us directly (for details see back page).

What is pre-eclampsia?

High blood pressure is common during pregnancy, but this does not usually cause any problems. Some women have protein in their urine as well as high blood pressure, and this is called pre-eclampsia. Most women with pre-eclampsia feel quite well but high blood pressure and protein in the urine are detected at routine antenatal checks. This rarely happens before five or six months of pregnancy, and often it is just days or a couple of weeks before the baby is due. If the condition starts early in pregnancy it is often more serious, as pre-eclampsia will tend to get worse until after the birth. It always disappears quite soon after delivery.

Occasionally women with pre-eclampsia have problems in their liver, kidneys, or blood clotting system. A few (about 1 in every 2000 pregnant women) will have a fit, and this is known as eclampsia. When this happens the woman usually needs careful nursing in hospital, and sometimes intensive care. The afterbirth (placenta) can also be damaged in pre-eclampsia. This may reduce the blood supply to the baby, which can prevent the baby from growing normally and sometimes leads to labour starting too early. If this happens the baby may need intensive care and will be more likely to have breathing problems, feeding difficulties or long term development problems.

The cause of pre-eclampsia is not known, but it seems to be due to a problem in the placenta which we do not fully understand yet.

Why use magnesium sulphate?

Once a woman has a fit (eclampsia) we know from recent research that magnesium sulphate is the best treatment to stop her having any more. Some doctors also give magnesium sulphate to women with pre-eclampsia, hoping that it will stop them having a fit and prevent some of the other problems of pre-eclampsia. For example, magnesium sulphate may help the woman's kidneys to work better and may help prevent the baby from being born too early. There is very little useful research into whether magnesium sulphate really is the best treatment. Although one study has suggested that it might be good for women, this was not conclusive and gave little information about the effects for the baby.

How is magnesium sulphate used?

Magnesium sulphate is given first as an injection into a vein, often on the back of the hand or in the arm. Treatment is usually continued for 24 hours either by putting the drug into a drip, or by regular injections into the muscle. Because the body gets rid of magnesium sulphate through the kidneys, the amount of urine is also measured. If the amount is small the woman may need less magnesium sulphate. Very rarely if too much magnesium sulphate is given it can cause a temporary muscle weakness, which can lead to breathing problems. To stop this happening reflexes and breathing rate are checked regularly. Sometimes there are side effects of magnesium sulphate. These can include nausea or vomiting, thirst, drowsiness and confusion, but they all disappear when treatment is stopped.

The Magpie Trial

This study is to try and find out whether magnesium sulphate stops women with pre-eclampsia having a fit. It will also test whether there are any immediate or future benefits of this treatment for the woman or the baby, and whether there are any important side effects. To do this, half the women in the study will be given a magnesium sulphate solution, and the other half will be given a similar solution without magnesium sulphate (a placebo).

If you decide to join this study which treatment you get will be decided randomly, rather like tossing a coin. This is so that magnesium sulphate can be tested fairly. Neither you, your doctor, nor your midwife will know if you are getting magnesium sulphate or placebo. In case your doctor needs to know, the information will be easily available by telephoning Oxford.

Your care will not be affected in any other way. There will be no extra hospital tests for either you or your baby. All the information for the study will be collected from the hospital notes, it will be confidential and used only by the researchers in the trial. We plan to follow up some of the women, and their children when they are older, to find out how they are. This means that if you agree to take part in the Magpie Trial we may write to you later.

Appendix 17

Ask your midwife to write the name of the local contact person for the Magpie Trial here

.....

If you would like any further information about the trial please contact

Magpie Trial Co-ordinating Centre
Institute of Health Sciences
Old Road
Headington
Oxford
OX3 7LF

Do you know about pre-eclampsia?

For further information about pre-eclampsia, contact the national charity Action on Pre-eclampsia

For written information, write with sae to:
APEC
31-33 College Road
Harrow, Middlesex
HA1 1EJ

For telephone support call the charity's Helpline
0181 427 4217
(Open weekdays, 10am – 1pm)

Some of this information is reproduced by kind permission of the charity Action on Pre-eclampsia (APEC)

MAGBR/1A01

The Magpie Trial: magnesium sulphate for treatment of pre-eclampsia, a study to evaluate the effects on women and their babies

What is pre-eclampsia?

- Pre-eclampsia is an illness that happens in pregnancy
- It is usually mild
- Sometimes it can be serious
- It can affect you and your baby
- It used to be called toxaemia

Who gets it?

Of every 100 pregnant women, 3 or 4 will get pre-eclampsia. You are more likely to get it if:

- This is your very first baby, or your first baby with a new partner
- You already have high blood pressure
- You are expecting twins, triplets, or more
- You had it early in your last pregnancy
- Any close relatives have had pre-eclampsia
- You have kidney disease or diabetes

How can it affect me and my baby?

- Pre-eclampsia can make your blood pressure higher than usual and give you protein in your urine
- It may also lead to other circulation problems
- Pre-eclampsia can stop your baby getting enough food or oxygen
- Your baby may grow more slowly and can develop other problems

How will I know if I have pre-eclampsia?

Pre-eclampsia usually starts in the second half of pregnancy. Signs that you may have it:

- Bad headaches that won't go away
- Bad pain just below your ribs, especially on the right side
- Blurred vision, flashing lights or spots in front of your eyes

What happens if I get pre-eclampsia?

- Identifying pre-eclampsia early makes it easier to keep you and your baby well
- Your blood pressure can be lowered with treatment
- You may be asked to stay in hospital, so that a close watch can be kept on the health of you and your baby
- Your baby may be delivered early
- Pre-eclampsia usually gets better quickly after your baby is born

What is the Magpie Trial?

- The Magpie Trial is a research study
- It is trying to find out if a simple drug called magnesium sulphate will help women with pre-eclampsia, and their babies
- The Magpie Trial involves hospitals throughout the UK and in many countries overseas

Am I likely to be involved in

- Your hospital is involved in the study
- Only women who are in hospital with pre-eclampsia will be invited to participate
- An information leaflet about the study is available in your hospital

We would like to let you know about the study. If you want to know more, ask your midwife or obstetrician, or contact us at the address overleaf.

The MAGPIE Trial: magnesium sulphate for treatment of pre-eclampsia, a study to evaluate the effects on women and their babies

The Magpie Trial is supported by the UK Medical Research Council, Department for International Development, World Health Organization and the European Commission

Appendix 18

Circumstances around the time of recruitment (speed of clinical situation, unpredictability of pre-eclampsia, difficult time to be approached):

Really quickly, I think I made it within five or ten minutes. I did not think about it that much because I was really out of it."

"I just said yes. He did give me information about it, but it was very traumatic at the time, so no I cannot really remember reading any of the information at that time, as within an hour I was in theatre."

"It was done in a hurry there was so little time to deal with everything that I don't think they could have gone into any more detail. It would have been nice to have gone into detail but given the circumstances it wasn't possible, so it's something I have to live with, I accept that it's just one of those things. Probably other people have had a chance to actually sit down and think about it and talk about it, I didn't but that was fine by me"

"A shock. I felt fine and as far as I was aware there was no immediate problems."

"I was surprised it came on at that stage, I thought it was like later on, when you got bigger and things like that. I did not really thing, I suppose you are not expecting it to happen to you and I had not had the warning signs right until then. So I was really shocked, I was shaking and I was really scared, really scared yes."

"It was a terrible shock for me, I was working on the Friday and as far as I was concerned I was months off having the baby and I was living a normal life and felt well. The next thing I was in hospital thinking I was going to have a really small baby within a week and maybe it might not survive. It was a really, really difficult time. I had so many things on my mind and we were so devastated just to be going into hospital at such an early time."

"I probably would have benefited from being told about the trial before. I understand that they did not know I was going to be pre-eclamptic"

"Someone actually coming and explaining what it is all about. A little bit more about pre-eclampsia. I had not a clue what it was about. I had not got a clue that it was potentially fatal. I did not know any of that. It would have been nice for someone just to sit down and give me some figures and explain women die of it. I did not have enough information in that way. I just think more information needs to be given really."

"I think I should have been made more aware of it before I actually took part in it. I knew nothing at all about it. I think probably in the last couple of months of my pregnancy I should have been told more about it. Well obviously parent classes or midwives, making them aware of trials that are taking place and informing them so that when you are having your checks or chats with the midwife they can explain the benefits, that you are running trials. Sometimes things don't go smoothly and I think if they knew about that before you may even get women asking, rather than you approaching them very cold and doing the cold sell from the beginning."

Appendix 18 continued

Women's understanding of the Magpie Trial (purpose of the trial, implications of joining Magpie, appreciation of possible risks, mixing usual care with trial care):

"I understood that they were trying to look into magnesium sulphate should be given as a treatment before you actually go into eclampsia and that is what they were testing and that they would give it to some people and not to others and then study the result of whether they actually went into eclampsia on the treatment."

"At the time, although it was a trial I just remember thinking well, I could get this drug that could prevent me fitting or I might not, or I might do, and therefore it has got to be worthwhile trying"

"I was just told there was a trial and some would be given magnesium sulphate and some would be given another injection to see if it worked, but you would not be told which one you were going to be given, that was all though"

" I thought it's a chance that you do get it [*magnesium sulphate*] and if I get the chance to bring my blood pressure down I was going to take the chance to do it"

"Because I am pleased that I did something that might benefit somebody else. I would hate to think, if they could stop somebody else going through what I did then I think that has got to be a good thing. Anything that stops people losing their babies to this thing is good. So I think it can only be a good thing"

"As I say, it is going to help others in the future and I am just a guinea pig really. If it is going to help one person, my participation in it, then that's great."

"I did not feel that there was going to be any harm. You knew there was someone there to help you. Because if there were any side effects, that I would be given something that would counteract those side effects."

"I was under the impression it was nothing particularly dangerous or it was quite safe."

"I suppose there is always a percentage of things, there could be side effects in years to come but I suppose you live for the moment and the moment was this may help me and I don't think I pondered on it too much. There was two things there, one it was going to benefit me two it was actually going to benefit a lot of other people. I think it's fair to say if they had said we don't know how this is going to affect your baby at all there could be serious consequences then I wouldn't. But I can't ever recall being told that or having that understanding so in my own mind I thought it"s minimum risk to myself now and in the future. It's something I'm going to do for now, that was the situation at the time."

"No they just went out and come in with the drips and put another drip into my arm and they put a catheter in and I wasn't sure if that was because of the trial or just because I had high blood pressure."

"No, I would have said no because the catheter was horrible I have never had a catheter in before but I know people who have and it was just horrible and you couldn't drink or anything and I was dying for a drink. I remember I hadn't eaten I went into the hospital on the Tuesday and the last meal I had was on the Monday night and the baby was born early hours Thursday morning. I hadn't eaten and I was starving I kept pinching fruit pastilles from my mum because I couldn't have a cup of tea because they were monitoring me. "

Appendix 18 continued

Methodological principles of randomised trials (random allocation, equipoise, uses of placebo, treatment blinding, thoughts on treatment allocation):

"They said there would be a 50-50 chance of you either getting the drug or not and she explained: 'well I could give you the drug or it could be water and you could react to them the same to both of them because you think it's the drug.' The way I thought that they wanted to give you the option to go into the trial and it was a 50-50 chance that you got the drug and if you thought you were getting that drug you would be more relaxed and it would bring your blood pressure down."

"I think the over ridding reassurance was that you were going to get it if you had a fit or were likely to fit and I think that was reassuring regardless of what you were on."

"You have to weigh up, if you put everyone on it and half worked and half did not then you could just think half did not. If all the one's you put on it worked or 90% and 2% of their blood pressure comes down then you can see the difference. You can see that it could work or would not. I do understand why."

"Another point that she did make was I said 'if this is so beneficial what happens if I do have a fit would I not be allowed this treatment because I was on the trial and I was maybe given the placebo?' and she said 'no if you were to have a fit that just over-rides everything and you would receive the treatment anyway'. So, that was reassuring as well. They said that they did not know either way whether you were receiving the treatment or not."

"From the point of view there has always got to be someone who doesn't receive the treatment and generally, ethically, if a drug is shown to be making such an improvement that the ones on the placebo are suffering they tend to stop the trial and say that's it. It's just part of medicine and that we are developing and will continue to develop and unless you do this sort of trial how will you know that it's the drug that is creating the change and not just the illness progressing or the person getting better".

"You cannot compare if everybody has the magnesium sulphate and nobody has nothing, there is nothing to compare it with is there?"

"She said you might have the placebo or you might not, we will never know because it is done like that. Basically that the research would go through and they will find out, because they use it a lot in America don't they? And it is proven to work out there. So it was just to see if they could use it here, and if it does bring it down and if it doesn't, then it has not done any harm"

"It was explained that a placebo would be given or I would not know whether it was going to be a placebo or the magnesium sulphate"

I am assuming you have to blind things so that you are absolutely certain that it makes a difference, one way or the other. However, I don't know enough about it. If you gave everyone magnesium sulphate and you found out what happened, but not everybody who gets pre-eclampsia fits, so I am assuming that you are having to take a percentage of however many people who fit are on it and how many people fit who are not on it and look and see if that actually made a difference."

She explained I would either be given a drug or a placebo. She explained what placebo meant. She said I would not know what I had been given. She said the trial would know. We just monitor you. She said if you have the drug and your blood pressure does exactly what we want it to, then we know it is working. If you have not, your blood pressure stays quite high for an amount of time afterwards. You will not know, you can find out when it is all finished, but you will not know what you have been given and none of the midwives who have given it to you will know what you have been given. It will affect the outcome, definitely you should not know what you are getting."

Appendix 18 continued

Women's views regarding the decision-making process (making the decision, difficulty with asking questions, voluntariness of joining, influences on decision-making, quality of information received, involvement of others in decision-making):

"Well it has only been afterwards that I wanted to ask questions, but at the time I don't think. Maybe if it was not such a traumatic situation. Maybe if I was just sitting on the ward and somebody came along and said would you consider going into a trial, I might have thought more of it and asked more, but no it was the circumstances for me. I think in hind-sight it probably would have been better a little earlier on."

"She just explained what it was all about. It was a national trial and it was a good thing. She explained it was more my decision and there was no pressure and they would not come back to me and ask again."

"I remember thinking she was lovely and she was very reassuring and persuasive is not the right word because that makes it sound as if she forced it on us. She gave a very good reasoned argument for being involved that made us confident about joining, you know. I was very comfortable with her, even though it was at a stressful time, I did not feel like what is this women doing here at this time, nothing like that, I felt very comfortable with her presence when she was talking to us. My recollection is that she explained what pre-eclampsia was, how it affected women widely. She did not talk to me about how it affected births, but I think that was for a very obvious reason because it would not have been nice to do that, to think I could lose baby. There was certainly nothing to frighten me."

"I knew there was a minimum risk of things going wrong, but I don't think they [*clinicians*] knew that much about it themselves. If they'd of been trained more on it, maybe that would have helped them, as it was a new thing. I mean about the trial now. I know pre-eclampsia has been out for a while, but it is just if they had been trained on it more. They could of helped mothers more, or if it was someone like yourself or a midwife who has been through the experience and someone there who dealt with just that side of it. They were just a bit I don't know they just didn't give me that much information back. Then I'm not so sure if that was they didn't want to worry me or concern me. You have to weigh up the pros and cons really."

"We all *[family]* talked about it, but they left the decision up to me. They were happy to support me whatever I decided. My husband said it was entirely up to me what I wanted to do."

"We *[partner]* talked about it and read the leaflet and he was of the same opinion: if it is possibly going to help then yes. Although I probably would have decided on my own, because I knew I could come out of it and then I would have talked to him when I saw him. I think at the end of the day it would have been my ultimate decision as it is my body."

"Just my husband. But I don't think he had a lot of say in it. I think I decided, I think I just literally said *[yes to]* it."

"I was on my own. I think in a perfect world it would have been helpful to talk about it with somebody. I'm not sure it would have made a difference because sometimes, a friend or relative might have said 'oh no don't have it', and that might have made the decision harder. You tend to think it would be easier to have someone to discuss it with and I'm not sure."

"Relative wise, nobody I was on my own. They were having trouble contacting my husband. I said have you got hold of [husband] yet and she was trying everything, so there was no member of family with me. I knew husband would not have minded because he would have been happy to go with whatever I decided to do."

Appendix 18 continued

Reflections of joining Magpie (receiving the Magpie Trial results, experiences of the follow up study):

When they sent out the information, the clippings that was quite interesting."

Yes, there were cuttings out of the papers. I think it was good."

"It was nice to see, no matter what I was given I had helped in something good and that makes you feel good and no one can give you that. No one can take that away from me, I have helped in that and if someone else goes into hospital now with pre-eclampsia, feeling the way I felt they can be helped. It is from me going yes, and that makes me feel good, it really makes me feel good. I have done that. Yes, I have helped other people. Not me on my own, thousands of women in labour but I have helped and this makes you feel good, it makes you feel good about yourself."

"I cannot remember actually. It was a while ago. I just now that they were good. I have them still. I have kept everything sent."

"I thought it was really good what they did with my baby. I think it was good for the baby and when we were sent the questionnaires to fill in the baby wasn't very good with his speech but I didn't think that anything he could or couldn't do was because of anything that he had been given or not given. It was good to see how much that he could do I think they should just do that anyway."

Totally happy. The follow up has been absolutely wonderful. I couldn't ask for more."

"I was impressed with the information that you got, we were asked about the questionnaire but there was always a number that you could ask for more information which I did follow up if you remember and then I think certainly, when the trial ended and you got the information I think that was a very good idea and that for me I felt I had been part of the success really, something that would benefit other people and I thought that was excellent the way it was conducted. I don't know if that's the case in normal trials because I don't see that side of it. I think I would be probably more likely to join a trial now."

To offer your services to do a testing for mums with two year's old, people would bite your hand off. I think you could do it freelance actually. That was so in-depth and something you are not normally likely to have. It is like the chap on the telly, Professor Winston and it was almost like that programme coming into your house. That to me was a treat."

He has seen health visitors before and things like that and it is just a routine kind of thing. It was quite interesting to see I found because he was doing things that I didn't know he could do that. It was quite surprising really. On the questionnaire it said get him to draw a line or a circle and he wouldn't do it for me. It was like can you draw that - "No". It was just this thing and it said: 'can do it', 'sometimes' and 'not yet'. So there was a few 'not yet' and when you came he did it and I had put he couldn't do that. I found that quite interesting. Seeing what he could do. I don't think you always take notice of what they are doing until somebody actually comes along and says 'can you do this?' and you think he can't do that, and they go and do it! It opens your eyes a bit to what they are capable of."

Appendix 19

Magpie Trial: results of follow- up for women and children

You may remember that some time ago, during your pregnancy when you had pre-eclampsia ('toxaemia'), you kindly agree to participate in a study called the Magpie Trial. In 2002 we sent you a summary of the results of that study. We then contacted you again, as part of a Follow Up Study, to invite you to tell us about how you and your child were doing. We would now like to tell you what we found.

What was the Magpie Trial?

You were one of over 10,000 women worldwide who agreed to take part in the Magpie Trial. This study found that when women are in hospital with pre-eclampsia, giving them a drug called magnesium sulphate reduced the risk they would have eclampsia, which is a seizure or fit. These study results were published in a journal called 'The Lancet' in June 2002.

What was the Magpie Trial Follow-up Study?

The results of the Magpie Trial were based on what happened whilst the women and their babies were in hospital. It is also important to find out what happens to the women and children after this, and to work out whether being given magnesium sulphate influences their health after they go home from hospital. Our Follow-Up Study asked women, and families, about how they and their children were doing around 2-3 years after the birth. You may remember you were asked to complete two questionnaires sent to you in the post. The questionnaires asked about your health, and your child's health. Some families were also offered a visit at their home in order to find out a little more, particularly about the children.

What did the Follow-up Study find?

The Follow-Up Study did not find clear evidence that giving magnesium sulphate to women with pre-eclampsia influenced their health or their children's health two years later. These results were published in a journal called the 'BJOG: an international journal of Obstetrics and Gynaecology' in March 2007.

How to find out more

If you would like to read the full reports of the Magpie Trial and its Follow-Up Study, you can get these through your local library or, if you have access to the internet, the papers are available free of charge at www.thelancet.com and www.blackwell-synergy.com/loi/bjo

The references are:

- Magpie Trial Collaborative Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet 2002; 359: 1877-90.
- Magpie Trial Follow Up Study Collaborative Group. The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia. Outcome for women at two years. BJOG 2007;114:300–309.
- Magpie Trial Follow Up Study Collaborative Group. The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia. Outcome for children at 18 months. BJOG 2007;114:289–299.

Thank you so much

You have helped find out whether giving magnesium sulphate to women with pre-eclampsia is beneficial and safe. This information is helping improve the care for women with pre-eclampsia and their babies, worldwide

Appendix 20

QUOTE Study results letter

Magpie Trial letterhead
Contact details for RS
QUOTE Study

Date

Woman's name & address

Dear (woman's name)

You may remember that during your pregnancy with (child's name) you had pre-eclampsia ('toxaemia'), and you kindly agreed to participate in a study called the Magpie Trial. As a follow on from this I came and talked with you about your involvement in the trial.

I remember our conversation really well and I hope you and (child's name) are keeping well. I recall what you had to say was very interesting and has been really helpful in finding out about the views of women involved in the trial. I spoke with 39 other women and I have now analysed all the interviews and included with this letter is a summary of the results and a copy of the full report. I remember you said you would like to be sent a copy of them.

If you would like to ask any questions about the Magpie Trial or the enclosed results please do feel free to contact me.

May I take this opportunity to thank you once again for initially joining the Magpie Trial and its follow up study, and taking the time to talk with me. Your involvement has helped enormously in trying to find out the best way to treat women with pre-eclampsia and their babies, worldwide.

With very best wishes for the future

Rebecca Smyth
Research Midwife

Appendix 21

Results of the QUOTE Study

Qualitative Understanding of Trial Experience

What did the interviews find?

Circumstances around the time of recruitment to the Magpie Trial were difficult for some women:
For many of the women it was evident they were asked to consider joining the Magpie Trial at a difficult time. Having pre-eclampsia came unexpectedly and as a consequence many felt unprepared. Many were anxious about their health and that of their baby and as a result found it difficult to take in all they were being told.

Women would have preferred to have been told earlier in their pregnancy about the Magpie Trial, but appreciated the difficulty with this:
Some women felt had they been informed earlier in their pregnancy about the Magpie Trial they would have understood it better. However, they did feel that perhaps knowing about the trial before they were eligible to join (i.e. before having pre-eclampsia) might have made them worried about what could only potentially happen to them. Some suggesting that they might not have read the information had they been given it as it did not relate to their situation at the time.

Women joined in order to receive better care for themselves and their baby, but also wanted to help future women with pre-eclampsia:
Many women joined Magpie because they thought the trial drug (magnesium sulphate) was risk free and would help their pre-eclampsia, even though at the time this was not fully known. Other reasons were to help find a treatment for pre-eclampsia and so help women in the future.

The difference between care related to the Magpie Trial and routine monitoring for pre-eclampsia was unclear:
Most women were recruited when they were having intensive monitoring (blood pressure checks, urine measured, restricted oral fluids, reflexes checked and a drip put in) for pre-eclampsia. Monitoring solely connected to the Magpie Trial was observation of breathing rate and an extra drip. These differences were not clear to many women.

Women appreciated being sent a copy of the Magpie Trial results:
Women were pleased to receive a copy of the trial results as many had wondered what the results were. They found them interesting to read and felt being sent a copy acknowledged the important contribution they had made to the Magpie Trial.

Women welcomed long-term follow up:
Women enjoyed being contacted for the follow up study. They found the postal questionnaires easy to complete. The questionnaire relating to their child's ability they found particularly interesting. For those that were visited at home to have their child assessed they found the assessment reassuring and enjoyable to watch.

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