



Magnesium sulphate
for treatment of pre-eclampsia:
a trial to evaluate the effects
on women and their babies

PROTOCOL

Summary

Pre-eclampsia is an important cause of morbidity and mortality for the woman and her child. Eclampsia, the occurrence of seizures superimposed on pre-eclampsia, is rare but associated with a far worse outcome than pre-eclampsia. Anticonvulsants are used for women with pre-eclampsia in the belief that they reduce the risk of eclampsia, and so improve outcome. Internationally there is controversy about whether an anticonvulsant should be given to women with pre-eclampsia. If one is used, however, magnesium sulphate seems to be the best choice even though there is little reliable evidence about the overall benefits and hazards.

The Magpie Trial is comparing magnesium sulphate with placebo for treatment of women with pre-eclampsia. Primary measures of outcome are eclampsia and death of the baby. Effects on other measures of serious maternal and neonatal morbidity will also be assessed, as will the use of health service resources. The estimated sample size is 14,000 women.

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Background

Pre-eclampsia, a multisystem disorder of pregnancy usually associated with raised blood pressure and proteinuria, complicates 2-8% of pregnancies¹. Although outcome is often good pre-eclampsia is a major cause of morbidity and mortality for the woman and her child². It accounts for an estimated one fifth of antenatal admissions³, two thirds of referrals to day care assessment units⁴, and a quarter of obstetric admissions to intensive care units⁵. Eclampsia is rare, affecting around 1 in 2000 deliveries in the UK for example, but is associated with a considerably higher morbidity and mortality⁶.

Anticonvulsants may be administered to women with pre-eclampsia in the belief that these reduce the risk of a seizure, and so improve outcome^{7,8}. There is considerable variation in clinical practice but if an anticonvulsant is used, magnesium sulphate has recently emerged as the most rational choice^{9,10,11}. As for all prophylaxis, however, there is a particular responsibility to ensure that it does more good than harm. If magnesium sulphate does reduce the risk of eclampsia, the potential for benefit is relatively low (unless there are other beneficial effects), as most women would not have convulsed anyway. This is important as very large numbers of women and babies could be exposed to prophylactic anticonvulsants. In the US, for example, 5% of pregnant women receive magnesium sulphate before delivery¹². If the same usage was applied in the UK, 35,000 women would be treated each year. However, the incidence of eclampsia is only about 400 women/year⁶ without the use of magnesium sulphate. So, even if magnesium sulphate halves this risk, 200 women might be protected from fitting but 34,800 would have been exposed to the possible adverse effects.

The first question to be answered is whether magnesium sulphate reduces the risk of eclampsia. Even if it does do so, before it can safely be introduced into clinical practice more information is required about: (a) the size of the risk reduction; (b) effects on other important outcomes for the woman and child; (c) disease severity at which benefits outweigh the risks and (d) the cost consequences of different forms of care. Magnesium sulphate is cheap and relatively easy to administer, but there could be a considerable cost for women, children and the health services if it is used routinely for pre-eclampsia without proper evaluation.

Systematic review of anticonvulsants for women with pre-eclampsia

A recent systematic review of randomised trials demonstrates that, currently, there is insufficient evidence to either support or refute the use of prophylactic anticonvulsants¹³. Twelve trials have evaluated anticonvulsants for women with pre-eclampsia. Two small studies were excluded from the review because either no clinical outcomes were reported, or they were not reported separately for pre-eclampsia and eclampsia^{14,15}. Two trials have compared magnesium sulphate with no anticonvulsant^{16,17} (228 women, South Africa; 64 women, Taiwan) and two have compared magnesium sulphate with placebo^{18,19} (822 women, South Africa; 135 women, USA). One quasi-randomised study (59 women, Tanzania)²⁰ compared oral diazepam with no anticonvulsant. The remaining trials compared magnesium sulphate with diazepam^{21,22} (38 women, Mexico; 28 women, Malaysia) or with phenytoin^{12,23,24} (2138 women, USA; 115 women, USA; 54 women, USA).

Results Overall, the methodological quality of these trials was average to poor. In most, concealment of the allocation at trial entry was inadequate, and two studies excluded from their analyses >10% of women randomised^{18,23}.

In the comparison of magnesium sulphate with no anticonvulsant/placebo, three women allocated magnesium sulphate had a fit, compared to 13 amongst those allocated no

anticonvulsant/placebo (Relative Risk 0.33; 95% CI 0.11-1.02). There was also a non-significant trend towards a small increase in the risk of Caesarean section for women allocated magnesium sulphate (RR 1.04; CI 0.92-1.17). There is little information about possible effects on other important outcomes. In the comparison of magnesium sulphate with phenytoin, women allocated magnesium were less likely to develop eclampsia (RR 0.09; CI 0.01-0.72), but more likely to have a Caesarean section (RR 1.21; CI 1.05-1.41). There were no statistically significant differences in stillbirths (RR 0.62; CI 0.27-1.41) or neonatal deaths (RR 0.84; CI 0.41-1.74) amongst the babies allocated magnesium sulphate rather than phenytoin *in utero*. There is little information about other relevant outcomes. No woman in the comparison of magnesium sulphate with diazepam developed eclampsia. No trials have reported follow-up of the children beyond the perinatal period, an economic evaluation, or an assessment of the costs to the health services.

Discussion To date, 1200 women with pre-eclampsia have been entered into trials comparing an anticonvulsant with none. The results of these trials, when taken together, are promising in terms of a reduction in the risk of eclampsia associated with the use of anticonvulsants. These data should be interpreted with caution, however, as the number of events was small and the largest study¹⁸ had a large proportion of post randomisation exclusions. Also, apart from the suggestion of a small increase in the risk of Caesarean section associated with the use of magnesium sulphate, there is little information about possible effects on other important outcomes, including toxicity and side effects. Nearly 2400 women have been randomised into trials comparing different anticonvulsants, most of whom were in one study comparing magnesium sulphate with phenytoin¹². Women allocated magnesium sulphate were less likely to fit than those allocated phenytoin but this study provides no insight into whether giving magnesium sulphate is preferable to withholding it. Also, the number of events was small (0 versus 10) and, apart from an increase in the risk of Caesarean section, there are few data on other measures of maternal morbidity. Finally, 1% of the women allocated phenytoin developed eclampsia. This is an unusually high incidence for the reported severity of disease (only 18% had $\geq 2+$ proteinuria and 4% had been given an antihypertensive) and may, at least in part, be due to chance.

In conclusion this review, combined with evidence that magnesium sulphate is the drug of choice for women with eclampsia²⁵, supports magnesium sulphate as the best choice of anticonvulsant to evaluate for women with pre-eclampsia. There is a suggestion that magnesium sulphate may be associated with an increase in the risk of Caesarean section, which may be a tocolytic effect²⁶. If true, this tocolytic action might have other consequences such as an increase in length of labour, postpartum haemorrhage and retained placenta.

Current use of prophylactic anticonvulsants

Internationally there is considerable variation in the use of anticonvulsants for women with pre-eclampsia. Amongst those who do use them, there is no consensus on either choice of agent or which women are most likely to benefit. In the USA, for example, 99% of obstetricians use magnesium sulphate which is given to an estimated 5% of pregnant women before delivery¹². In contrast, 23% of UK obstetricians never use any prophylactic anticonvulsants²⁷. In the past, only 2% used magnesium sulphate, others preferring diazepam, phenytoin or chlormethiazole^{6,28,29}. There has recently been a substantial shift towards using magnesium sulphate in the UK, with 40% of obstetricians now reporting that they use it²⁷.

Mode of action for magnesium sulphate

Exactly how magnesium sulphate might control eclamptic convulsions is unclear. Magnesium may have a localised cerebral effect. For example, it may cause vasodilatation with subsequent

reduction of cerebral ischaemia¹⁵, and/or block some of the neuronal damage associated with ischaemia^{30,31}.

A possible mechanism for vasodilatation is relaxation of smooth muscle, and it has been suggested that magnesium may have a generalised effect on all smooth muscle, including the peripheral vasculature and uterus. Alternatively, any effects of magnesium sulphate in control of eclamptic convulsions may be, wholly or partially, through its role as a blocker of N-methyl-D-aspartate (NMDA) receptors in the brain. These NMDA receptors are activated in response to asphyxia, leading to calcium influx into the neurones which causes cell injury. It is suggested that magnesium may block these receptors, so reducing calcium influx and protecting the neurones from damage.

Possible benefits of magnesium sulphate

Magnesium sulphate may reduce the risk of eclampsia. This effect may be reflected in a lower risk of other complications of eclampsia, such as renal failure, cerebrovascular accident and liver failure, as well as improved blood pressure control. If real, these potential benefits may lead to less time spent in hospital and less use of intensive care facilities.

Suggestions about the possible mode of action for magnesium sulphate have also led to hypotheses about potential benefits for children who are exposed while *in utero*. For example, if magnesium sulphate administration does delay progression of pre-eclampsia this may be reflected in a reduction in preterm delivery. The mechanism for such a reduction could be either later onset of spontaneous labour or less obstetric intervention. In addition, it has been suggested that magnesium sulphate administration may improve the outcome for asphyxiated babies³². For preterm babies, exposure to magnesium sulphate may also be associated with a lower risk of cerebral haemorrhage³³, which in turn could be reflected in a reduction in the risk of cerebral palsy for these low birthweight infants^{34,35,36}. All these hypotheses are based on observational data and, although they are being tested in randomised trials, these data await confirmation^{37,38}.

Possible hazards of magnesium sulphate

Potential hazards of magnesium sulphate include, for the woman, respiratory depression, respiratory arrest and hypotension³⁹. Cardiac arrest is a theoretical risk, but in practice is likely to be rare as a complication of magnesium sulphate. If magnesium does relax smooth muscle it may also have a tocolytic effect²⁶ leading to an increase in a length of labour, postpartum haemorrhage, retained placenta and blood transfusion. In addition, potential side effects include nausea, vomiting, thirst, flushing of the skin, hypotension, arrhythmias, drowsiness, confusion, and muscle weakness. We therefore need reassurance that magnesium sulphate, when used for women with pre-eclampsia, is well tolerated. Also magnesium sulphate may have an effect on mood post partum and so it is important to check whether it has any influence on the incidence of postpartum depression.

For the baby, possible hazards related to hypermagnesaemia are similar to the mother and include respiratory depression, hypotonia and hypotension^{32,40}. Recently it has been suggested that *in utero* exposure to magnesium sulphate for prevention of preterm delivery may increase the risk of mortality for the baby⁴¹, when compared to other tocolytic agents. However there are several other possible explanations for these data, as the number of events was very small and there were imbalances between the treatment groups^{37,38}. Also, the dose of magnesium sulphate was very high (median 49.5g). Whatever the effects of magnesium sulphate on the outcome for low birthweight children, reassurance will still be required about possible effects for bigger babies, as the pathophysiology of cerebral palsy in these two groups is very different³⁶.

Why is a trial needed now?

In 1995, magnesium sulphate was shown to be the anticonvulsant of choice for women with eclampsia²⁵ (see table). These results had a major impact on both practice and policy throughout the world. Magnesium sulphate for the treatment of eclampsia is now included in the essential drugs list of the World Health Organisation and is recommended in the practice guideline produced by the Royal College of Obstetricians and Gynaecologists, London.

Data from the Collaborative Eclampsia Trial on maternal deaths and recurrence of convulsions

	MgSO ₄ n=453	Diazepam n=452	RR (95% CI)	MgSO ₄ n=388	Phenytoin n=387	RR (95% CI)
Death	*17 (3.8%)	*23 (5.1%)	0.74 (0.40-1.36)	10 (2.6%)	20 (5.2%)	0.50 (0.24-1.05)
Further fits	60 (13.2%)	126 (27.9%)	0.48 (0.36-0.63)	22 (5.7%)	66 (17.1%)	0.33 (0.21-0.53)

RR = relative risk; CI = confidence interval; * outcome not known for 1 woman

Having switched to magnesium sulphate for women with eclampsia, many clinicians are also reviewing their policies for anticonvulsant prophylaxis. As discussed above further evidence is required to help them decide whether its use would be beneficial and, if so, for whom. Nevertheless many clinicians have begun using magnesium sulphate for women with pre-eclampsia, and others are considering starting to use it. There is currently a window of opportunity for properly evaluating this use of magnesium sulphate. Results of the Magpie Trial will provide a reliable basis for decision-making about the care of women with pre-eclampsia.

Outcomes to monitor and size of benefits to be detected in the Magpie Trial

In the Magpie Trial, sufficient women with pre-eclampsia will be randomised to provide really reliable evidence about the effects of magnesium sulphate on substantive outcomes. As outlined above, only a very small proportion of women will develop eclampsia, even amongst those with severe pre-eclampsia. Perinatal death and other adverse maternal or neonatal events are also relatively uncommon. Very large numbers of women will therefore have to be studied to provide reliable estimates of the effects of magnesium sulphate on these outcomes. The aim is to find out if, overall women and/or their children do better if they get magnesium sulphate rather than placebo, regardless of whether treatment is started before or after delivery and irrespective of any previous anticonvulsant therapy.

Sample size estimates For women with severe pre-eclampsia the risk of convulsions is around 1%. To demonstrate a halving in this risk would require 14,000 women (alpha 0.05, beta 0.1). The aim is therefore to recruit 14,000 women. The trial may include women with a lower seizure risk and, if this was 0.75%, the power to demonstrate a halving would then be 80%. Most women (90%) are likely to be randomised before delivery and, if total mortality for the babies was 12%, this would give a power of 90% to detect a 15% proportional reduction to 10.2% (alpha 0.05). If total mortality for the babies was reduced from 10% to 8.5% (15% reduction), the power would be 80% (alpha 0.05).

Trial Procedures

All trial materials and guidelines for their use are provided in the Magpie Trial Folder supplied by the Co-ordinating Centre. What follows here is a brief summary of the trial procedures.

Who can be entered into the Magpie Trial?

The criteria for trial entry outlined below are the **minimum** requirements for blood pressure and proteinuria. Most women entered into the trial will have higher blood pressures and more proteinuria. As about a quarter of women with eclampsia have only moderate rises in blood pressure at the time of their first fit, however, these criteria will ensure that such women are not excluded.

Women **are** eligible for trial entry if:

- there is clinical uncertainty about whether magnesium sulphate would be beneficial*
and
- not delivered, or delivered within the last 24 hours
and
- blood pressure today ≥ 90 mmHg diastolic or ≥ 140 mmHg systolic, on at least two occasions
and
- proteinuria of at least 1+
and
- consent has been given

* uncertainty is likely to be influenced by the presence of signs or symptoms of imminent eclampsia, such as hyperreflexia, frontal headache, blurred vision and epigastric tenderness.

☞ If the woman's initial blood pressure does not require immediate treatment, the two measurements should be taken 30 minutes apart, but up to one hour between measurements is allowed. If the initial blood pressure is high enough to require consideration of immediate antihypertensive treatment, the second measurement should be taken in less than 30 minutes.

☞ Whenever possible, use a mid-stream urine sample to assess proteinuria, and exclude infection as a cause of the proteinuria.

Women are **not** eligible for trial entry if:

- the attending clinician believes magnesium sulphate should either be given or withheld
or
- the woman does not wish to be randomised, for whatever reason
or
- hypersensitivity to magnesium
or
- hepatic coma with a risk of renal failure
or
- myasthenia gravis

- ☛ Women with renal impairment (urine output <25ml/hour) can be randomised if the clinician is uncertain about the value of magnesium sulphate, but the volume of trial treatment should be halved for each dose. Women with prolonged oliguria should only continue treatment if their reflexes and respiration are normal.
- ☛ If tendon reflexes are slow or the respiratory rate is reduced but the clinician would still consider magnesium sulphate therapy, the woman can be entered into the trial but the volume of trial treatment should be halved for each dose.

Trial entry

Whenever possible, women should be informed about the study and have an opportunity to see the information leaflet (Appendix 1) before being asked to participate. This leaflet has been developed in consultation with women who have had pre-eclampsia and representatives of UK-based consumer groups, including Action on Pre-Eclampsia (Apec) and the National Childbirth Trust (NCT). After being invited to join the Magpie Trial women should, whenever possible, have the opportunity to discuss the trial with relatives and those responsible for their clinical care. Some women may change their mind after trial entry and request that trial treatment be stopped. This request must be respected, but complete follow-up information is still required to maintain the integrity of the trial.

Once she has agreed to participate in the study (a suggested consent form is provided: Appendix 2) the randomisation procedure will depend on which system is most practicable in the hospital; the telephone randomisation service or the local pack system. Identical sealed treatment packs are provided for both systems. Numbered boxes, each containing eight numbered treatment packs, are distributed to collaborating hospitals by the Co-ordinating Centre in Oxford. The combination of box and pack number forms a unique identifier for each woman.

Hospitals with access to the 24-hour telephone randomisation service Women are entered into the trial by means of a telephone call to the 24-hour randomisation service in Oxford. During this telephone call brief baseline details from the Trial Entry page in the Women's Booklet (Appendix 3) are requested, and recorded on a computer, before the treatment allocation can be given. At the end of the call a two-digit pack number (and the four digit number of the box from which it should be taken) is issued, and this number should be recorded **immediately**. Once this pack number is allocated, the woman is irrevocably entered into the trial, irrespective of whether the treatment pack is opened.

Randomisation is balanced for major prognostic variables; severity of pre-eclampsia, gestational age at randomisation, whether delivered, whether given anticonvulsants drugs before trial entry, whether a multiple pregnancy and country.

Hospitals using a local pack system This system is only for hospitals that do not have access to the 24-hour telephone randomisation service. When a woman has given consent to participate in the trial the clinician completes the Trial Entry page in the Women's Booklet (Appendix 4). This page must be completed **BEFORE** the treatment pack is opened, it records brief baseline details about the woman **and** the number of the next treatment pack. The treatment packs **MUST** be used in the order in which they are removed through the slot in the box, which is lowest number first. Once the Trial Entry page has been completed the woman is entered into the trial, irrespective of whether the treatment pack is opened.

Trial treatment

As soon as a woman has been allocated a treatment pack, the pack is opened and the trial treatment inside given as directed. Each treatment pack contains 9 x 10ml ampoules of either 50% magnesium sulphate (5g per ampoule; 1g/2ml) or placebo, 1g ampoule of calcium gluconate (10ml) in case of toxicity, and an Eclampsia Rescue Pack. Participating hospitals choose whether to use the intravenous or the intramuscular route for maintenance therapy. All other aspects of care are at the discretion of the attending clinician.

The safe use of magnesium sulphate relies on careful monitoring of tendon reflexes, respiratory rate and urine output. Before the trial treatment is started, the clinician checks:

- knee or other tendon reflexes are present
- respiratory rate is normal (>16 respirations/minute)
- urine output was >100ml over the last 4 hours, or >25ml/hour

☞ If tendon reflexes are slow, respiratory rate is reduced but the woman is well oxygenated, or urine output is <25ml/hour treatment can be started, but with half the stated volume of trial treatment for each dose.

If using the **INTRAVENOUS** route for maintenance therapy

To give the loading dose Take 8ml from ampoule 1, dilute with normal saline as usual, and give IV over 10-15 minutes.

To give maintenance therapy Take 10ml from ampoule 2, dilute with normal saline as usual, and give as an IV infusion equivalent to 2ml trial treatment/hour. Continue for 24 hours using ampoules 3-6. Ampoules 7-9 are extra, use if needed.

If using the **INTRAMUSCULAR** route for maintenance therapy

To give the loading dose Take 8ml from ampoule 1, dilute with normal saline as usual and give IV over 10-15 minutes. Take 10ml from ampoule 2 and inject IM into one buttock, then take 10ml from ampoule 3 and inject into the other buttock.

To give maintenance therapy Give 10ml IM into alternate buttocks every 4 hours, using ampoules 4-8. This is 24 hours' treatment, and means the last dose is given 20 hours after the loading dose. Ampoule 9 is extra, use if needed.

Subsequent care for all women entered into the trial should be based on the assumption that they were given magnesium sulphate.

If the pack is finished but treatment needs to be continued or restarted

For some women, the attending clinician may wish to either continue treatment for longer than is possible with one treatment pack, or to restart treatment sometime later. In these situations the woman must **not** be randomised a second time. The 24-hour randomisation service should be contacted to allocate an additional treatment pack, which will contain the same treatment as the first.

Hospitals using the full 24-hour randomisation service An Additional Treatment form (Appendix 7) should be completed before the telephone call is made to the randomisation service. During the telephone call the brief details requested on the form will be recorded on the computer prior to an additional treatment pack allocation being given. The additional pack number should be recorded on the form **immediately**.

Hospitals using a local pack system Hospitals using a local pack system to enter a woman in to the trial should use the telephone randomisation service to request an additional treatment pack, as described above.

If the randomisation service **cannot** be accessed, the clinician must decide whether or not to use unblinded magnesium sulphate. The use of any non-trial anticonvulsant treatment is recorded on page two of the Follow-up section of the Woman's Booklet (Appendix 5).

Clinical monitoring

Trial treatment should only be continued if the following criteria are satisfied

- knee or other tendon reflexes are present
 - respiratory rate is normal (>16 respirations/minute)
 - urine output in the last 4 hours was >100ml
- ☞ Check reflexes and respiration every 30 minutes, or according to your usual practice.
- ☞ Urine output should be measured hourly for the duration of treatment.
- ☞ If tendon reflexes are slow, respiratory rate is reduced but the woman is well oxygenated, or urine output is <100ml in 4 hours but it is considered appropriate to continue with trial treatment, use half the stated volume of trial treatment for each dose.

Serum monitoring is **not** required. Serum levels should only be measured on the rare occasion the attending clinician considers this necessary. If levels are done, this should be recorded on page one of the Follow-up section of the Woman's Booklet. Random checks will be arranged with the laboratories in hospitals with access to magnesium levels.

Toxicity

Complications of magnesium sulphate therapy, such as respiratory depression or respiratory arrest, may occur either because of magnesium toxicity or as complications of severe pre-eclampsia. These should be managed as normal for each hospital. The following guidelines are provided for management of magnesium toxicity:

Respiratory arrest, due to magnesium toxicity Stop the trial treatment and initiate usual emergency procedures. Intubate the woman or insert an airway, and ventilate immediately. Give 1g calcium gluconate (10ml) by slow intravenous injection, over 10 minutes. Continue ventilation until the resumption of normal spontaneous respiration.

Respiratory depression, due to magnesium toxicity Stop the trial treatment. Give oxygen by mask. Maintain the airway and nurse in the recovery position. If necessary, give 1g calcium gluconate (10ml) by slow intravenous injection, over 10 minutes.

Absent tendon reflexes, due to magnesium toxicity Stop the trial treatment. If respiration is normal, monitor reflexes until they return to normal. If respiration is depressed, manage as above. Only consider restarting trial treatment when reflexes return to normal, and then use half the volume of trial treatment for each dose.

Urine output <100ml in 4 hours If there are no other signs of toxicity, reduce the volume of subsequent doses of trial treatment by half. When there are other signs of toxicity, manage as for the appropriate section above. Review the woman's overall management with particular attention to fluid balance.

What to do if the woman has eclampsia

In the event of eclampsia, emergency care is to give an intravenous bolus of 2-4g magnesium sulphate. Each treatment pack contains an Eclampsia Rescue Pack with two red labelled ampoules. One ampoule is 5g magnesium sulphate and the other, marked Eclampsia Ampoule, has 10ml of either magnesium sulphate 50% or placebo. These allow treatment with magnesium sulphate to begin without needing to know what the woman was given in the trial.

- **Control the acute fit**

Take 2-4ml from each ampoule, dilute with saline as normal, and give IV over 5-10 minutes.

This means that women who had active treatment in the trial will get 1-2g magnesium sulphate, while those who had placebo will get 2-4g magnesium sulphate.

- **Stop trial treatment**

- **Start maintenance therapy according to local practice**

For IV maintenance therapy Begin an infusion of 1g/hour magnesium sulphate. Continue as normal in your hospital.

For IM maintenance therapy Wait until the next IM dose is due, then give 5g magnesium sulphate IM. Continue maintenance therapy with 5g every 4 hours, or as normal in your hospital.

- ☞ If further fits, repeat the bolus of 2-4g magnesium sulphate IV over 5-10 minutes as required.
- ☞ Continue clinical monitoring as in the trial.

The woman's care should be based on the assumption that she was given magnesium sulphate within the trial. This will avoid over treatment, minimising the risk of toxicity. All other aspects of care should be determined by normal clinical practice.

Follow-up of the women and babies

It is crucial that follow-up is as complete and as accurate as possible for all women entered into the study. Information about what happened to the women after trial entry and outcome for the liveborn babies should be collected in the Woman's Booklet (see Appendix 5 and 6). The top copies of each sheet should be returned promptly to the Co-ordinating Centre. If either the woman or the baby is transferred to another hospital, these details are requested on the relevant form. The Co-ordinating Centre will then contact this hospital to find out what happened after transfer.

Unblinding the trial treatment

For most women, unblinding of the trial allocation is not necessary, even after eclampsia. In the rare event of particular clinical concern when the attending clinician feels unblinding is in the woman's best interests, this can be done by telephoning the 24-hour randomisation service.

Serious unexpected events

After trial entry, clinical events are recorded in the Follow-up (Appendix 5) and Liveborn Baby sections (Appendix 6) of the Women's Booklet. A Serious Unexpected Event form (Appendix 8) is provided, but should **only** be used to notify events that are considered sufficiently serious and unexpected that the Co-ordinating Centre needs to be notified immediately.

Analysis

Description of the women entered into the trial

The Magpie Trial will address questions about effectiveness for a wide range of women. The women entered into the Magpie Trial will be heterogeneous, but the extent of this clinical heterogeneity will be described by the characteristics recorded at trial entry. In addition, the women will be classified into sub-groups on the basis of clinically important characteristics at trial entry:

- whether they had severe pre-eclampsia
- whether they had already had an anticonvulsant
- whether they had already delivered
- whether they were <33 completed weeks gestation

Defining the severity of pre-eclampsia

For the purposes of this trial, women are considered to have severe pre-eclampsia at trial entry if, either:

- diastolic blood pressure ≥ 110 mmHg on 2 occasions **or**
- systolic blood pressure ≥ 170 mmHg on 2 occasions **plus**
- $\geq 3+$ proteinuria
- or**
- diastolic blood pressure ≥ 100 mmHg on 2 occasions **or**
- systolic blood pressure ≥ 150 mmHg on 2 occasions **plus**
- $\geq 2+$ proteinuria **plus**
- at least two signs or symptoms of imminent eclampsia
- or, if given antihypertensive agent <48 hours before trial entry**
- highest diastolic blood pressure in 48 hours before trial entry ≥ 110 mmHg **or**
- highest systolic blood pressure in 48 hours before trial entry ≥ 170 mmHg **plus**
- $\geq 3+$ proteinuria at trial entry
- or**
- highest diastolic blood pressure in 48 hours before trial entry ≥ 100 mmHg **or**
- highest systolic blood pressure in 48 hours before trial entry ≥ 150 mmHg **plus**
- $\geq 2+$ proteinuria **plus**
- at least two signs or symptoms of imminent eclampsia

An additional subgroup analysis will compare outcome for women who have two or more signs or symptoms of imminent eclampsia with outcome for women who have hypertension and proteinuria alone.

Principal comparisons for the assessment of treatment

The main trial comparisons will involve assessment of the effects of magnesium sulphate on:

- **Eclampsia** (a fit, and any recurrent convulsions)
- **Stillbirths and infant deaths before discharge from hospital** (for women entered before delivery)
- **Maternal deaths** (although the number of such deaths is likely to be small)
- **Serious maternal morbidity** (respiratory depression, respiratory arrest, cardiac arrest, coagulopathy, renal failure, liver failure, pulmonary oedema and cerebral haemorrhage)

Subsidiary comparisons will assess the effects of magnesium sulphate on:

- **Use of maternal health service resources** (number of days in hospital and in an intensive care unit, ventilation, dialysis, anticonvulsant and antihypertensive therapy)
- **Complications of labour and delivery** (for women entered before delivery: induction and length of labour, Caesarean section, retained placenta, blood loss, transfusion, gestation at delivery)
- **Neonatal morbidity** (for women entered before delivery: Apgar at 5 minutes, intubation at place of delivery, ventilation, supplemental oxygen for >24 hours, abnormal cerebral ultrasound, convulsions)
- **Use of neonatal health service resources** (for women entered before delivery: days in special care baby unit, length of ventilation)
- **Toxicity** (need for calcium gluconate, stopped or reduced treatment due to toxicity, stopped or reduced treatment due to side effects)
- **Side effects of magnesium sulphate** (nausea or vomiting, flushing of the skin, drowsiness, confusion, muscle weakness, abscess)

At centres where follow-up of the children would be feasible, information is being collected to ensure that, if indicated, this would be possible. Follow-up is provisionally planned for when the children are 4 years old. In a separate study, risk of postnatal depression will be assessed at 3 months by sending a postal questionnaire to a subgroup of women randomised within the UK.

Type of analysis

All analyses will be based on the groups as randomly allocated, in other words this will be an intention-to-treat analysis. For the principal comparisons statistical significance will be taken as the 5% level, and for the subsidiary comparisons the 1% level. In addition to the pre-specified sub-group analyses, sensitivity analyses will explore whether compliance with the allocated treatment influences the size of any effects on the primary outcomes. Good compliance, defined as loading dose plus 20-28 hours maintenance therapy, will be compared to both higher and lower doses. The effect of >12 hours treatment will be compared to ≤12 hours treatment.

Data monitoring

During recruitment data will be monitored, in confidence, by an independent data monitoring committee. The data monitoring committee is responsible to the steering committee and, although it may communicate certain interim analyses to the steering committee or suggest certain protocol changes, the steering committee will remain responsible for deciding which changes to adopt.

Whilst recruitment to the Magpie Trial is ongoing, interim results will be supplied, in strict confidence, to the chair of the data monitoring committee as frequently as requested. Meetings

of the committee will be arranged periodically as considered appropriate by the chair but at least annually. In the light of the interim data, and of any other evidence or advice they wish to seek, the data monitoring committee will inform the chair of the steering committee if, in their view: (i) there is proof beyond reasonable doubt that - either for all women or for any particular category of women - treatment with magnesium sulphate is clearly indicated or contra-indicated, and there is a reasonable expectation that this new evidence would materially influence patient management, or (ii) it is evident that no clear outcome will be obtained. Proof beyond reasonable doubt may be taken as a difference of at least 3 standard deviations in at least one of the primary outcomes. This has the practical advantage that the exact number of interim analyses is not important.

Trial organisation

Magpie Trial Co-ordinating Centre The Co-ordinating Centre is based at the Institute of Health Sciences, Oxford. The co-ordinating team is responsible for all aspects of trial administration, including supply of trial materials and treatment packs, data management, and the analyses. They are also responsible for providing a 24 hour on-call service to deal with problems and queries related to the study, and for ensuring that all collaborating hospitals are regularly updated regarding progress of the trial.

South African Co-ordinating Centre The South African Co-ordinating Centre is based in Durban. This regional centre is responsible for raising trial awareness within South Africa, co-ordinating data collection, maintaining trial recruitment within South Africa, and facilitating communication between the South African collaborating hospitals and the Co-ordinating Centre in Oxford.

Argentinean Co-ordinating Centre The Argentinean Co-ordinating Centre is based in Rosario/Buenos Aires. This regional centre is responsible for raising trial awareness within Spanish speaking hospitals in South America, co-ordinating data collection, maintaining trial recruitment, and facilitating communication between the collaborating hospitals and the Co-ordinating Centre in Oxford.

Trial management

Magpie Trial Steering Committee The overall progress of the trial will be monitored by a scientific and administrative steering committee. The membership of this committee is: Rory Collins, Lelia Duley, Edmund Hey, Richard Lilford, Jack Moodley, James Neilson, Stephen Robson, Peter Rubin (Chair), James Thornton, Sara Twaddle, and Isabel Walker. Observers are Marc de Bruycker, Barbara Farrell, Marian Kelly and José Villar. The UK Medical Research Council convenes this committee.

Magpie Trial Management Group This group will meet every 2-3 months to assist with day to day running of the trial, and to prepare reports for the steering committee. Membership: Mike Clarke, Lelia Duley, Barbara Farrell (Chair), James Neilson, Jane Notman and Patsy Spark.

Data Monitoring Group The terms of reference of the data monitoring committee are outlined earlier. The membership of this committee is: Richard Doll (Chair), Adrian Grant (Vice Chair), Naren Patel, Jimmy Volmink and Godfrey Walker.

International Advisory Board An International Advisory Board has been convened to advise the Magpie Trial Management Group, as and when requested. This board has a multidisciplinary membership from around the world.

Funding

The trial is jointly funded by the UK Medical Research Council, the UK Department for International Development, the World Health Organisation, and the European Commission.

Active ampoules

The magnesium sulphate used in this trial has been obtained from a single supplier. Each 10ml 'active' ampoule contains 5g magnesium sulphate heptahydrate ($\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$) 50% solution, which is approximately 2mmol magnesium/ml.

Indemnity

The following is a statement from the UK Medical Research Council outlining their position on indemnity:

'The MRC as a sponsor of a trial or work involving human subjects accepts responsibility attached to its sponsorship of the work, and as such would give sympathetic consideration to claims for any non-negligent harm suffered by a person as a result of participating in a trial or other work. This would not extend to liability for non-negligent harm arising from conventional treatment where this is one arm of a trial. The Council acts as its own insurer and does not provide advance indemnity cover for participants in MRC-funded studies.'

'Where studies are carried out in a hospital, the hospital continues to have a duty of care to a patient being treated within that hospital, whether or not that patient is participating in an MRC-supported study. The MRC does not accept liability for any breach in the hospital's duty of care, or for any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS trust or not.'

The Magpie Trial is indemnified under the University of Oxford's clinical trial insurance policy, which provides indemnity to both the University and those acting directly under its auspices in respect of procedures and practices laid down in the trial protocol. The magnesium sulphate used in the Magpie Trial, and its placebo, carry a product indemnity provided by the supplier.

Medicines Control Agency

The Medicines Control Agency has provided a DDX certificate to cover doctors working on the trial within the United Kingdom.

Proposed policy for publication and authorship

The success of the Magpie Trial depends upon the active collaboration of a large number of people, particularly the co-ordinators and other staff in each of the participating hospitals. For this reason, authorship of any presentations or reports related to the trial will be in the name of the collaborative group, and the final trial report will name local co-ordinators as well as those involved in central co-ordination and trial management. Inevitably, for journal publication it is not possible to name everyone who has contributed to a study such as this. Certificates of collaboration will be provided to those who have made a substantial contribution but whose name is not on the final report.

The results will be presented, in confidence, to the collaborators before publication. Once the final report has been published, collaborators may have access to the data from their hospital for additional descriptive analyses. Outcome by treatment group will not be presented for individual centres in the main reports of the Magpie Trial.

Satellite studies

Proposals for subsidiary studies linked to the Magpie Trial are welcome, and should be presented to the Trial Management Group for discussion and approval.

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Appendix 1:

INFORMATION LEAFLET

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.

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.

Your decision

You may want to think a bit more about whether to take part, and discuss it with your partner or someone else. If you agree to join the study, it is important to start the treatment soon. You can change your mind at any time if you wish to by asking your doctor or midwife to stop the treatment, but we would still like to be able to contact you later if necessary. If you do decide to join the study we will tell your GP that you are taking part and send him details about the Magpie Trial.

If you decide not to join

Whatever your decision, it will not affect any other aspect of your care.

If you need more information

If you would like more information about this study, please ask your doctor or midwife, or contact the Magpie Trial Coordinating Centre.

Thank you

Appendix 2:



Consent

I have read the Information Leaflet for the Magpie Trial and have no more questions. **I am willing to take part in this study.** I understand that the treatment can be stopped at any time, if I request it, without this affecting my medical care in any other way.

Name: _____

Woman's signature

Date

 / /
Assent by another person

I have read the Information Leaflet for the Magpie Trial and have no more questions. **I agree that** _____ (name of woman) **should take part in the Magpie Trial.** I understand that the treatment can be stopped at any time, if requested, without this affecting her medical care in any other way.

Signature of person giving assent

Date

 / /

Relationship to woman _____

Woman's verbal consent

The woman named below has read the Information Leaflet, or has been given the information verbally, and has agreed to participate in the Magpie Trial. **She is willing to take part in this study.** She understands that she can stop the treatment at any time, if she requests it, without this affecting her usual medical care.

Name of woman _____

Witness's signature
(e.g. doctor or midwife)

Date

 / /
Thank you

Appendix 3:



Trial Entry

Please collect the following information **BEFORE** telephoning the randomisation service **+44 (0) 1865 240972 or 0800 585323 (UK Only)**

Country: Hospital name: or Hospital code:

Name of responsible clinician:

Has consent been given? Yes

Hospital Record Number: Date of admission:
(If UK centre give NHS number if known) day month year

Family name: Given name/s:

Date of birth: If not known, estimated age: years
day month year

THE FOLLOWING QUESTIONS WILL BE ASKED BY NUMBER OR LETTER

1. Is/was this a multiple pregnancy? Yes No

2. Has the woman already delivered? Yes No Other *please specify*

If the woman has already delivered go to Question 5

3. EDD (Estimated Date of Delivery) **AND** Best estimate of gestational age completed weeks
(if known) day month year

4. If not delivered, is a fetal heart beat present? *(Continue on separate sheet if more than three babies)*

a) Baby one	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Not known <input type="checkbox"/>
b) Baby two	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Not known <input type="checkbox"/>
c) Baby three	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Not known <input type="checkbox"/>

5. Blood Pressure: (must meet eligibility criteria)

1st measurement: Systolic /Diastolic mmHg

2nd measurement: Systolic /Diastolic mmHg

6. Proteinuria (must be at least +1): + number

	YES	NO	
7. Does the woman have frontal/severe headache?	<input type="checkbox"/>	<input type="checkbox"/>	
8. Does the woman have epigastric pain?	<input type="checkbox"/>	<input type="checkbox"/>	
9. Does the woman have blurred vision?	<input type="checkbox"/>	<input type="checkbox"/>	
10. Does the woman have hyperreflexia and/or clonus?	<input type="checkbox"/>	<input type="checkbox"/>	
11. Does the woman have oliguria (<25ml urine/hour)?	<input type="checkbox"/>	<input type="checkbox"/>	<i>If the answer is YES, the dose needs to be reduced</i>
12. Does the woman have a history of epilepsy?	<input type="checkbox"/>	<input type="checkbox"/>	Unknown <input type="checkbox"/>
13. Has she had any antihypertensive drug/s in the last 48 hours?	<input type="checkbox"/>	<input type="checkbox"/>	Unknown <input type="checkbox"/>
a) If Yes , what was her highest BP in the last 48 hours? <small>(exclude the two measurements in Question 5)</small>	<input style="width: 20px; height: 15px; border: 1px solid black;" type="text"/>	<input style="width: 20px; height: 15px; border: 1px solid black;" type="text"/>	Systolic <input style="width: 20px; height: 15px; border: 1px solid black;" type="text"/> <input style="width: 20px; height: 15px; border: 1px solid black;" type="text"/> <input style="width: 20px; height: 15px; border: 1px solid black;" type="text"/> /Diastolic <input style="width: 20px; height: 15px; border: 1px solid black;" type="text"/> <input style="width: 20px; height: 15px; border: 1px solid black;" type="text"/> mmHg
14. Has she had any anticonvulsant drug/s in the last 48 hours?	<input type="checkbox"/>	<input type="checkbox"/>	Unknown <input type="checkbox"/>
a) If Yes , has she had magnesium sulphate during this time?	<input type="checkbox"/>	<input type="checkbox"/>	Unknown <input type="checkbox"/>

The allocated treatment pack number is

If this pack number is unavailable or damaged please telephone again for a new allocation

Thank you

MAG/TR/1/998

Appendix 4:



Trial Entry

Women are eligible for entry if:

- ✓ Not delivered, or delivered within the last 24 hours
- ✓ Blood pressure ≥ 90 mmHg diastolic or ≥ 140 mmHg systolic on at least two occasions
- ✓ Proteinuria of a least +1
- ✓ Uncertainty about whether magnesium sulphate would be beneficial
- ✓ Consent has been given

Women are not eligible for entry if:

- ✗ Hypersensitivity to magnesium sulphate
- ✗ Hepatic coma with a risk of renal failure
- ✗ Myasthenia gravis

Complete this form BEFORE you take a treatment pack from the box

Country: Hospital name: or Hospital code:

Has consent been given? Yes

Hospital Record Number: (if known) Date of admission: / /
day month year

Family name: Given name/s:

Date of birth: / /
day month year If not known, estimated age: years

1. Is/was this a multiple pregnancy? Yes No
2. Has the woman already delivered? Yes No Other *please specify*

If the woman has already delivered go to Question 5

3. EDD (Estimated Date of Delivery) / /
(if known) day month year **AND** Best estimate of gestational age completed weeks

4. If not delivered, is a fetal heart beat present? (*Continue on separate sheet if more than three babies*)

- | | | | |
|---------------|------------------------------|-----------------------------|------------------------------------|
| a) Baby one | Yes <input type="checkbox"/> | No <input type="checkbox"/> | Not known <input type="checkbox"/> |
| b) Baby two | Yes <input type="checkbox"/> | No <input type="checkbox"/> | Not known <input type="checkbox"/> |
| c) Baby three | Yes <input type="checkbox"/> | No <input type="checkbox"/> | Not known <input type="checkbox"/> |

5. Blood Pressure: (must meet with eligibility criteria) 1st measurement: Systolic / Diastolic mmHg
 2nd measurement: Systolic / Diastolic mmHg

- | | | | |
|---|--------------------------|--------------------------|--|
| 6. Proteinuria <small>(must be at least +1):</small> + <input type="text"/> number | YES | NO | |
| 7. Does the woman have frontal/severe headache? | <input type="checkbox"/> | <input type="checkbox"/> | |
| 8. Does the woman have epigastric pain? | <input type="checkbox"/> | <input type="checkbox"/> | |
| 9. Does the woman have blurred vision? | <input type="checkbox"/> | <input type="checkbox"/> | |
| 10. Does the woman have hyperreflexia and/or clonus? | <input type="checkbox"/> | <input type="checkbox"/> | |
| 11. Does the woman have oliguria (<25ml urine/hour)? | <input type="checkbox"/> | <input type="checkbox"/> | |
| 12. Does the woman have a history of epilepsy? | <input type="checkbox"/> | <input type="checkbox"/> | Unknown <input type="checkbox"/> |
| 13. Has she had any antihypertensive drug/s in the last 48 hours? | <input type="checkbox"/> | <input type="checkbox"/> | Unknown <input type="checkbox"/> |
| a) If Yes , what was her highest BP in the last 48 hours? Systolic <input type="text"/> <input type="text"/> / Diastolic <input type="text"/> <input type="text"/> mmHg
<small>(exclude the two measurements in Question 5)</small> | <input type="checkbox"/> | <input type="checkbox"/> | Unknown <input type="text"/> <input type="text"/> mmHg |
| 14. Has she had any anticonvulsant drug/s in the last 48 hours? | <input type="checkbox"/> | <input type="checkbox"/> | Unknown <input type="checkbox"/> |
| a) If Yes , has she had magnesium sulphate during this time? | <input type="checkbox"/> | <input type="checkbox"/> | Unknown <input type="checkbox"/> |

If the answer is YES, the dose needs to be reduced

Now take the next treatment pack and write the pack number here

Date form completed / / Time form completed : 24 hour clock

Person completing this form (PLEASE PRINT)

Fax TOP copy of this form IMMEDIATELY to the Magpie Trial Co-ordinating Centre.

Fax: +44 (0) 1865 227173

Thank you

MAG/BR/1/998

Appendix 5:



FOLLOW-UP

Page ONE

Complete when the woman is discharged; at six weeks after delivery or at death; whichever occurs first

Country: Hospital name: or Hospital code:
 Hospital Record No: Number of treatment pack used:
(first pack allocated)
 Family name: Given name/s:
 Date of birth: / / or, if not known, estimated age: years
day month year

INFORMATION TO BE COLLECTED AFTER TRIAL ENTRY

TRIAL TREATMENT

Was trial treatment started? Yes No

If **No**, reason:

If **Yes**, date and time **started**

/ /
day month year :
24 hour clock

date and time **stopped**
(if IM, record time of last injection)

/ /
day month year :
24 hour clock

* How many ampoules were used?

* Total volume of trial treatment given (exclude any diluent)

ml

Was the trial treatment reduced at any time? Yes No

If **Yes**, reason:

Was the trial treatment restarted? Yes No

Was trial treatment discontinued early (<24 hours)? Yes No

If **Yes**, give main reason (*tick (✓) one box ONLY*)

- woman asked that it be stopped
- oliguria/renal failure
- respiratory depression/arrest
- tendon reflexes absent
- side effects
- other

please specify:

Was an additional treatment pack requested? Yes No

If **Yes**, was the treatment given? Yes No

If **Yes**, number of treatment pack used

date and time **started**

/ /
day month year :
24 hour clock

date and time **stopped**
(if IM, record time of last injection)

/ /
day month year :
24 hour clock

number of ampoules used from this pack

total volume of trial treatment given from this pack (exclude any diluent)

ml

Were there any side effects of trial treatment? Yes No

If **Yes**, what were they?

Were there problems at the injection site for trial treatment? Yes No

If **Yes**, what were they?

Were serum magnesium level/s measured during trial treatment? Yes No

If **Yes**, reason

* See Guidelines

Appendix 5: Continued

Follow-up — Page TWO

OTHER TREATMENT FOR PRE-ECLAMPSIA, given after trial entry

Was any ward stock magnesium sulphate given for pre-eclampsia? Yes No

If **Yes**, reason:
 how much was given? g

Were any other anticonvulsant/s given for pre-eclampsia? Yes No

If **Yes**, which?

Were any antihypertensive drug/s given for pre-eclampsia? Yes No

If **Yes**, which?
 date first given / /
day month year

THIS PREGNANCY

Number of previous pregnancies lasting ≥20weeks

Was the woman given steroids in the seven days before delivery? Yes No

If **Yes**, date the last dose was given / /
day month year

Did she have a placental abruption? Yes No

If **Yes**, did this occur after trial entry? Yes No Not sure

For Office Use

COMPLICATIONS FOR THE WOMAN

1. Did she have eclampsia? Yes No

If **No**, go to question 2

If **Yes**, date of first fit / /
day month year number of fits

was the Eclampsia Rescue Pack used? Yes No

If **Yes**, how much was she given from each ampoule? Magnesium sulphate: ml

Eclampsia Ampoule: ml

was she given any other anticonvulsant/s after the first fit? Yes No

If **Yes**, which?

was she given antihypertensive drug/s after the first fit? Yes No

If **Yes**, which?

2. Did she have any other problem/s after trial entry? (tick (✓) relevant box) Yes No

respiratory depression <input type="checkbox"/>	respiratory arrest <input type="checkbox"/>
pneumonia <input type="checkbox"/>	pulmonary oedema <input type="checkbox"/>
cardiac arrest <input type="checkbox"/>	* cerebrovascular accident <input type="checkbox"/>
* renal failure <input type="checkbox"/>	* liver failure <input type="checkbox"/>
* coagulopathy <input type="checkbox"/>	other <input type="checkbox"/>
	please specify

Was she given calcium gluconate? Yes No

Was she admitted to an intensive care unit? Yes No

If **Yes**, date of admission / /
day month year date of discharge /
day month year

Was she admitted to an obstetric high dependency area/unit? Yes No

If **Yes**, date of admission / /
day month year date of discharge /
day month year

* See Guidelines

Appendix 5: Continued

Follow-up — Page THREE

For Office Use

Was she artificially ventilated? Yes No
 If Yes, how long for? total days
 Did she have renal dialysis? Yes No
 If Yes, how long for? total days
LABOUR AND DELIVERY – Was she discharged before delivery? Yes No
 * If Yes, go to page 4
 * Was labour augmented? Yes No
 * Was labour induced? Yes No
 Did the woman have a vaginal delivery? Yes No
 If Yes, date and time of onset of labour / / :
day month year 24 hour clock
 What was the best estimate of gestational age at delivery? completed weeks
 Date and time of delivery / / :
day month year 24 hour clock
 Did she have a manual removal of placenta? (Answer NO if ceasean section) Yes No
 * What was the best estimate of blood loss at delivery? (enter NK if not known) ml
 Did she have a blood transfusion after trial entry? Yes No
 Did she have a platelet transfusion after trial entry? Yes No

What was the mode of delivery?

	Baby 1	Baby 2	Baby 3
spontaneous vaginal	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
forceps/ventouse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Caesarean section before labour	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Caesarean section in labour	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
vaginal breech	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Was the baby,

	Baby 1	Baby 2	Baby 3
stillborn?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
liveborn?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

What was the birthweight?

	Baby 1	Baby 2	Baby 3
g	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>

What is the sex?

	Baby 1	Baby 2	Baby 3
M <input type="checkbox"/> F <input type="checkbox"/> U <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If the baby was liveborn,

	Baby 1	Baby 2	Baby 3
what was the Apgar at 5 minutes?	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
was s/he intubated at place of delivery?	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>

If the baby was stillborn,

	Baby 1	Baby 2	Baby 3
was s/he macerated?	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
what was the likely cause of death?

	Baby 1	Baby 2	Baby 3
was a post mortem examination done?	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>

If Yes, please send a copy of the report to the Co-ordinating Centre when available

If more than three babies please complete this section in another booklet

Please remember to complete the 'Liveborn Baby' section

* See Guidelines

Appendix 5: Continued

Follow-up — Page FOUR

PLEASE COMPLETE ONE OF THE FOLLOWING

1. If the woman is still in the trial hospital six weeks after delivery

reason

2. If the woman died

date of death / /
day month year

main cause of death:

other contributing factors:

was a post mortem examination done? Yes No

If Yes, please send a copy of the report to the Co-ordinating Centre when available

3. If the woman was discharged from the trial hospital

date of discharge / /
day month year

where to: home other reason:

If she was discharged home, please give the full postal address

Address:

Post/Zip code:

If she was discharged/transferred to another hospital/clinic, give the following information

Name of hospital/clinic:

Address:

Post/Zip code:

Telephone:

Fax:

If UK centre please give GP name and address

Name:

Address:

Post/Zip code:

Telephone:

Fax:

Name of contact person (PLEASE PRINT)

If anything is known about what happened to the woman, please inform the Co-ordinating Centre

*** If the woman was discharged before delivery, complete another Follow-up section in another booklet AFTER delivery**

Person completing this form:

(PLEASE PRINT)

Today's date / /
day month year

Please send the TOP copy of ALL four pages to the Co-ordinating Centre using the addressed envelope provided, or fax: +44 (0) 1865 227173

For Office Use

Thank you

Appendix 6:



Liveborn Baby

Complete one form for each liveborn baby either at discharge; at six weeks after delivery, or at death, whichever occurs first

Country: Hospital name: or Hospital code:

Mother's family name: Mother's given name/s:

Number of treatment pack used for mother: (if known) Baby's Hospital Record Number: (if known)

Baby's family name: Baby's given name/s:

Baby's date of birth: / / * Baby 1 Baby 2 Baby 3

Was the baby admitted to special/intensive care (e.g. SCBU, NICU)? Yes No

If **Yes**, date of admission / / date of discharge / /

Was the baby artificially ventilated (e.g. IPPV, CPAP)? Yes No

If **Yes**, how long for? total days to date

Did the baby have a convulsion/s (fit/seizure)? Yes No

Did the baby have cerebral imaging before discharge? Yes No

If **Yes**, was there: ventriculomegaly? Yes No

evidence of parenchymal damage? Yes No

For Office Use

Please describe any serious complications, including congenital malformations:

Please complete one of the following sections

1. If the baby is still in hospital at 6 weeks, reason

2. If the baby died date of death / /

Main cause of death: congenital malformation details

(tick (✓) one box only) asphyxia

prematurity

other please specify

Was a post mortem examination done? Yes No

If **Yes**, please send a copy of the report to the Co-ordinating Centre when available

3. If the baby was discharged/transferred from the trial hospital

Date of discharge/transfer / / Discharged home? Yes No

If discharged/transferred to another hospital/clinic, give the following information

Name of hospital/clinic:

Address:

Post/Zip code:

Telephone: Fax:

Name of contact person (PLEASE PRINT)

If anything is known about what happened to the baby, please inform the Co-ordinating Centre

Person completing this form: (PLEASE PRINT)

Today's date / /

Please send the TOP copy to the Co-ordinating Centre using the addressed envelope provided, or fax: +44 (0) 1865 227173

* See Guidelines

THANK YOU

MAG/LB/2/699

Appendix 7:



Additional Treatment Form

IF YOU REQUIRE AN ADDITIONAL TREATMENT PACK FOR A WOMAN WHO IS ALREADY PARTICIPATING IN THE MAGPIE TRIAL PLEASE COMPLETE THIS FORM

**NOW TELEPHONE THE RANDOMISATION SERVICE
+44 (0) 1865 240972 or 0800 585323 (UK ONLY)**

Country: Hospital name: or Hospital code:

Name of responsible clinician:

WOMAN'S DETAILS

Hospital Record Number:
(if known)

Family name: Given name/s:

Date of birth: / /
day month year If not known, estimated age in years

Box and Treatment Pack Number allocated at entry (if known):
Box Pack

Date treatment from the initial pack started: / /
day month year

Reason for further treatment: Continuation of original treatment
 Second episode requiring treatment

From box number Take treatment pack number
If this pack is unavailable or damaged telephone again to get another pack number

***If this pack is not used for this woman DISCARD IMMEDIATELY
File this form in the woman's notes***

**Magpie Trial Co-ordinating Centre
Institute of Health Sciences
Old Road, Headington
Oxford OX3 7LF
United Kingdom
Tel: +44 (0) 1865 226642
Fax: +44 (0) 1865 227173**

Thank you
MAG/AT/1/898

Appendix 8:



Serious Unexpected Event Form

This form should **only** be used to notify events that are sufficiently serious and unexpected that the Co-ordinating Centre needs to be notified immediately. All other events, including eclampsia, should be recorded in the Women's Booklet.

When this form has been completed telephone the randomisation service to report the event
+44 (0) 1865 240972 or 0800 585323 (UK only)

Country: Hospital name: Hospital code:

Name of responsible clinician:

Contact telephone number:

WOMAN'S DETAILS

Hospital Record Number:
(if known)

Family name: Given name/s:

Date of birth: / / If not known, estimated age in years

day month year

Box and Treatment Pack Number allocated at entry (if known):
Box Pack

Date of delivery (if delivered): / /
day month year

DETAILS OF SERIOUS UNEXPECTED EVENT (tick (✓) one box ONLY)

Did it involve the woman? Did it involve the baby? Did it involve both woman and baby?

Date it occurred: / /
day month year

Brief summary of what happened:

Person completing this form: (PLEASE PRINT)

Date form completed: / /
day month year

Now you have reported the event, fax the completed form to the Co-ordinating Centre. If fax is not possible, make a copy and send by first class mail to:

**Magpie Trial Co-ordinating Centre
 Institute of Health Sciences
 Old Road, Headington
 Oxford OX3 7LF
 United Kingdom**

**Tel: +44 (0) 1865 226642
 Fax: +44 (0) 1865 227173**

THANK YOU

***Magpie Trial Co-ordinating Centre
Institute of Health Sciences
Old Road, Headington
Oxford OX3 7LF
United Kingdom***

***Telephone: +44 (0) 1865 226642
Fax: +44 (0) 1865 227173
Email: magpie@ndm.ox.ac.uk***