MAGNESIUM IN CORONARIES (MAGIC)

A STUDY OF THE EFFECT OF MAGNESIUM ADMINISTRATION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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I. HYPOTHESIS OF THE STUDY

Intravenous magnesium will reduce the short-term mortality of high-risk patients with suspected acute myocardial infarction when it is administered sufficiently early to reduce reperfusion injury.

II. INTRODUCTION AND BACKGROUND

The management of patients with acute myocardial infarction (MI) has improved dramatically over the last three decades. Advances in the general coronary care unit environment, treatment with beta blockers, and aggressive attempts at reperfusion have all contributed to a reduction in mortality from acute MI[1]. Large randomized trials have demonstrated that aggressive reperfusion strategies in conjunction with aspirin can reduce mortality in patients with suspected acute MI to an average of 6.5% to 7.5%[2]. However, as seen in Table I, the mortality rate remains high in two particular subgroups of patients: those over 65 years who receive thrombolytics (13.5% to 24%)[2-7] and those of any age who do not receive thrombolytics (11.5% to 13%).

Recently, attention has turned to additional adjunctive pharmacologic treatment with agents such as magnesium, nitrates, and angiotensin converting enzyme inhibitors to determine their potential for reducing mortality further. Of these, magnesium appears to be particularly promising. It is safe, even in the hands of physicians who have no prior experience with it, and it is easily administered and readily available. Further, if it has the expected benefit in the high-risk groups described above it would become an unusually cost-effective intervention, costing less than $2,500 per year of life saved. The following paragraphs present the rationale for this trial.

Possible cardiovascular consequences of magnesium deficiency

Animal and clinical studies[8] have shown that magnesium deficiency can lead to multifocal necrosis with calcium accumulation in mitochondria in a pattern reminiscent of myocardial ischemia. It can also lead to cardiomyopathy, atherogenesis, a heightened tendency to platelet aggregation, sinus tachycardia and repolarization abnormalities, as well as ventricular tachyarrhythmias. Reduced serum magnesium may also be responsible for a maladaptive increase in coronary tone and an increased response to vasoconstrictors[9]. Patients with acute MI may be deficient in magnesium, especially if they have a low dietary intake, are of advanced age, or are on diuretics.

Potential cardioprotective effects of magnesium

The rationale for supplemental administration of magnesium very early after the onset of acute myocardial infarction is provided by abundant data indicating potential cardioprotective effects of magnesium [10-12]. Magnesium protects myocytes against calcium overload by inhibiting calcium influx, an important problem at the time of reperfusion[12]. In experimental models of ischemia and reperfusion, agents inhibiting calcium influx improved post-ischemic recovery of mechanical function when given prior to, or at the time of, reperfusion. On the other hand, little improvement in mechanical function was observed if such agents were given 15-20 minutes after the onset of reperfusion [13]. Other potential cardioprotective mechanisms of magnesium have been demonstrated experimentally, including: reduced vulnerability to oxygen-derived free radicals[14], reduced myocardial oxygen demand mediated via sinus slowing and lowering of blood pressure[15], coronary vasodilation, enhancement of collateral development[16], and inhibition of platelet aggregation[17].

In the setting of acute myocardial infarction, when increased levels of available magnesium might be beneficial, there is actually a decline in free magnesium. This decline is due to a sharp rise in free fatty acids resulting from catecholamine-induced lipolysis at the onset of chest pain that results in a complexing of magnesium in the form of insoluble soaps[15]. Thus, although total body magnesium does not decrease, magnesium available in a free form that is capable of exerting a cardioprotective effect declines. Hence, there is a strong theoretical rationale for supplemental magnesium administration early in acute myocardial infarction.

Review of RCT experience

Since 1984, at least 10 randomized control trials (RCTs) of intravenous magnesium for acute MI have been reported. Several statistical models exist for pooling the data from multiple RCTs in a meta-analysis and estimating the treatment effect of magnesium. It is important to review the essential features of these models in order to place the RCT

findings in proper perspective. The fixed effects model assumes that the RCTs are sampled from a homogenous group of trials. Under the homogeneity assumption, each RCT provides an estimate of the true treatment effect and differences between the estimates from the various RCTs are due only to experimental error (within-trial variability). The random effects model assumes the RCTs are heterogeneous and that differences between their estimates of the treatment effect are due both to experimental error (within-trial variability) and real differences among the trials such as trial design and characteristics of the patients enrolled (between-trial variability)[18]. The random effects model is generally favored since heterogeneity that cannot be explained by experimental error often exists among RCTs, and this model takes such heterogeneity into account in estimation and hypothesis testing[19].

Meta-analyses of the seven RCTs published between 1984-1991 provided an estimated odds ratio (OR) for mortality of magnesium-treated patients of 0.44 (0.27-0.71) using the fixed effects model and 0.45 (0.23-0.86) using the random effects model[20,21]. The Leicester Intravenous Magnesium Intervention Trial (LIMIT-2), published in 1992[22], reported a 24% reduction in mortality with magnesium treatment ($P<0.04$), confirming the benefit of magnesium in reducing mortality in MI and inspiring many clinicians to advocate magnesium treatment programs in their coronary care units. The magnesium-treated patients in LIMIT-2 experienced a 25% lower incidence of congestive heart failure in the coronary care unit, suggesting that magnesium exerts its beneficial effects, at least in part, via a direct protective action on the myocardium. Given the potent predictive power of left ventricular function on survival following MI, one would anticipate that magnesium-treated patients in LIMIT-2 would have a lower long-term mortality. This hypothesis appears to have been confirmed by the recent long-term follow up report from LIMIT-2 showing a 21% lower rate of ischemic heart disease-related mortality in the magnesium group over a median follow up of 2.7 years[23]. The LIMIT-2 investigators have recently examined the mortality rates over a five year follow up, and continue to document the same long-term benefit of magnesium when administered in the acute phase of infarction[24]. The absence of any loss of the mortality benefit of magnesium over the long-term is consistent with a significant

myocardial protective effect achieved during the critical period of myocardial reperfusion.

The results of ISIS-4 seemed to contradict the results of the above studies. A total of 58,050 patients were enrolled in ISIS-4: 29,011 allocated to magnesium and 29,039 to control. There were 2,216 deaths (7.6%) by 35 days in the magnesium group and 2,103 deaths (7.2%) in the control group (OR 1.06[0.99-1.13]) suggesting no mortality benefit of magnesium administration and even the possibility of slight harm[25]. The findings of ISIS-4 have triggered considerable controversy over the reasons why it produced a null effect for magnesium in reducing mortality in suspected acute myocardial infarction[26,27].

When ISIS-4 is added to the preceding RCTs, the fixed effects model (driven heavily by the large sample size of ISIS-4) indicates no beneficial effect of magnesium (OR= 1.02 [0.96-1.08]). The random effects model takes into account the heterogeneity among these trials and suggests that magnesium may reduce mortality (OR= 0.59[0.39-0.90])[28] (See Figure 1). Thus, the random effects model suggests that one must search for possible sources of differences between ISIS-4 and the preceding trials. Two important differences that appear to be acting in concert to bias ISIS-4 toward a null effect of magnesium include:

- a low control group mortality, and
- magnesium was administered late

1. A low control group mortality rate. The control group mortality in ISIS-4 was only 7.2%. This was probably the result of the extensive use of thrombolysis (70% of patients) and antiplatelet agents (94% of patients) combined with the enrollment of intrinsically low-risk patients (only 2% were over 70 years of age, 17% had a history of a prior MI, 14% had clinical CHF, and 2% had SBP < 100 mm Hg). Incremental mortality-reducing effects of magnesium are difficult to detect against a low control mortality rate. The inability of ISIS-4 to detect any overall benefit of magnesium also applies to specific subgroups such as the 17,325 patients who did not receive thrombolytics. ISIS-4 had less than 60% power to detect even a 10% reduction observed in the 9.3%

control mortality in this subgroup. A detailed analysis relating the mortality rate in the control group and the treatment effect of magnesium observed in the clinical trials published before ISIS-4 clearly shows that the benefit of magnesium therapy increases as the control group mortality increases. Using this relationship, it was predicted that trials with a control group mortality rate of about 7% would show no benefit of magnesium therapy, precisely the result observed in ISIS-4[27,28]. Of note, the LIMIT-2 trial observed a control group mortality of 10.3% that was reduced to 7.8% with magnesium. The ISIS-4 control group mortality was thus below that of the magnesium-treated group in LIMIT-2.

This analysis is consistent with the results of the latest RCT recently reported by Shechter and colleagues[29]. They randomized 194 patients, 98 to placebo and 96 to intravenous magnesium. All 194 patients presented with acute MI and were considered unsuitable for thrombolysis. In addition to the standard contraindications to lytic therapy, reasons for exclusion from thrombolysis included presentation after 6 hours and/or age greater than 70 years.

Shechter et.al.[29] reported 17 deaths (17.3%) in the placebo group and 4 deaths (4.2%) in the magnesium group corresponding to an OR of 0.21 (0.07-0.64). The causes of death in this study were consistent with the hypothesis that magnesium helps reduce mortality by a direct myocardial protective effect. In the placebo group, 11 patients died from cardiogenic shock, 2 from electromechanical dissociation, 2 from myocardial rupture and 1 from cardiac arrest. By contrast, in the magnesium group, 1 patient died of cardiogenic shock, 1 from myocardial rupture, and 2 from electromechanical dissociation. Particularly noteworthy are the findings in the subset of 77 patients over the age of 70, a group expected to have a high short-term mortality from acute MI. Indeed, 10 of the 44 elderly patients treated with placebo died (23%), while only 3 of the 33 elderly patients treated with magnesium died (9%, p=0.09). Also, in this higher-risk subgroup, the incidence of congestive heart failure was reduced from 25% in the placebo-treated patients to 18% in the magnesium-treated patients.

2. Magnesium was administered late in ISIS-4. The ISIS-4 protocol required that acute phase treatments for MI, including lytic therapy, were administered prior to randomization, therefore initiation of study drug therapy (i.e., magnesium) could not be in the "early" lytic phase (e.g., first hour)[25]. Although the time from the onset of symptoms to randomization was recorded in ISIS-4, time from randomization to actual administration of magnesium was NOT recorded. The median time to randomization from the onset of chest pain for all patients was 8 hours. In the subset of patients who did not receive thrombolytic therapy (30% of trial patients), the median time to randomization from the onset of chest pain was a prolonged 12 hours. The ISIS-4 investigators have reported no further details of the distribution of time to randomization.

In an effort to answer concerns about timing of events, the ISIS-4 investigators conducted a retrospective survey of 1,000 randomly selected patients. This survey revealed that among those receiving thrombolytics, only about 50% received magnesium within two hours following the start of thrombolytic therapy. In LIMIT-2, the median was 3 hours from the onset of chest pain to initiation of treatment; and in Schechter's study[29] of the non-thrombolytic-treated patients, the average time from chest pain to initiation of treatment was about 7 hours in both the treatment and placebo groups (a full five hours earlier than in the non-thrombolysed group in ISIS-4).

Attempts at subgroup analyses in ISIS-4 also suffer from the critical lack of precise information on the time of administration of magnesium. Although no apparent benefit of magnesium was seen in the 23,000 patients randomized within six hours of the onset of chest pain, or among the 17,000 who did not receive thrombolytic therapy (including 9,000 randomized within 12 hours), most of these patients received magnesium several hours after randomization. One cannot be confident that reperfusion (pharmacologically-induced or spontaneous) took place in the presence of a raised serum magnesium level in any subgroup.
Experimental attempts aimed at ameliorating cellular calcium overload have shown that calcium antagonists must be administered before reperfusion, or during a critical

window of only a few minutes following reperfusion, in order to minimize contractile dysfunction. Calcium flux inhibitors, such as magnesium, administered after reperfusion appear to be ineffective[30,31].

The same observations pertain to the subset of patients, alluded to by the ISIS-4 investigators, who were randomized within six hours of symptom onset and had a high multivariate adverse prognosis score. In the absence of details on the timing of administration of magnesium, the findings of the ISIS-4 study remain compatible with the hypothesis that early administration of magnesium (particularly before reperfusion occurs) is associated with a reduction in mortality from acute myocardial infarction.

Conclusion: The implications of these observations are that, in order to prevent calcium overload of reperfused myocytes, a loading dose of magnesium should be administered before reperfusion therapy (pharmacological or mechanical) or, in patients not receiving reperfusion therapy, during the period when spontaneous reperfusion is most likely to occur. The design of ISIS-4 did not permit these conditions to be met. Prior studies suggest the low-risk profile that characterized the majority of ISIS-4 patients may have precluded beneficial results. The results recently reported by Shechter et.al.[29] suggest that high-risk MI patients benefit from an early infusion of magnesium.

The conflicting results of prior trials mean that the effectiveness of magnesium remains uncertain. Potential explanations of the varying results suggest that timing of therapy and patient risk level are key factors in determining magnesium effectiveness. In light of the potential effectiveness, ease of implementation, and low cost of this therapy, there is an urgent need to complete a trial that will assess the effectiveness of early administration of magnesium in higher risk patients. MAGIC is designed as this trial.

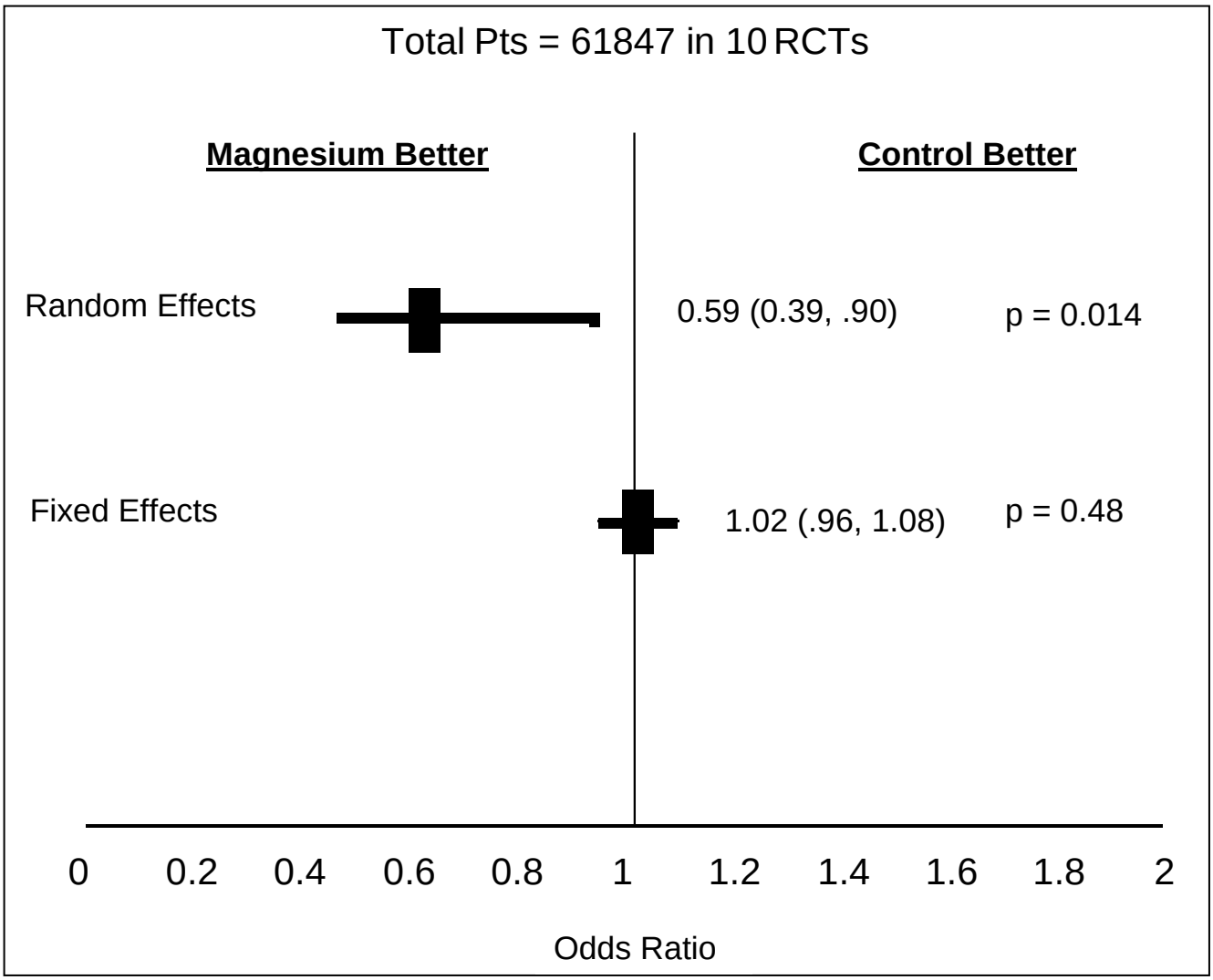
TABLE I

In Hospital and 35-day Mortality of Different Patient Subgroups

Patient Subgroup	Mortality Rate (%)	Number at Risk	Reference
Thrombolytic Therapy			
Age 65-74	13.5% (35 days)	8487	FTT[2]
Age ≥ 75	24.3% (35 days)	2835	FTT[2]
No Thrombolytic Therapy			
All subgroups	13.1% (in hospital)	156,512	NRMI[3]
All subgroups	11.5% (35 days)	29,285	FTT[2]
BBB	23.6% (35 days)	1025	FTT[2]
ST elev anterior	16.9% (35 days)	6642	FTT[2]
ST depression	13.8% (35 days)	1784	FTT[2]

Figure 1

Meta-Analysis of RCTs of Magnesium for MI: Fixed vs. Random Effects Models



III. OBJECTIVES OF THE STUDY

A. Primary objective

To determine if administering intravenous magnesium within 6 hours of symptom onset in high-risk patients with suspected acute MI reduces all cause 30-day mortality. Treatment will be initiated sufficiently early in an attempt to reduce reperfusion injury. For patients receiving reperfusion therapy, study treatment will be given before or during thrombolysis or PTCA. For patients not receiving reperfusion therapy, study treatment will be given within the 6-hour window, at a time before spontaneous reperfusion is likely to occur.

B. Secondary objectives

1. To define the mechanisms of benefit from magnesium treatment, by assessing the need for treatment of:
    a. Cardiogenic shock
    b. Congestive heart failure
    c. Ventricular fibrillation or sustained ventricular tachycardia
2. To assess the tolerability of magnesium by comparing the treatment groups with respect to:
    a. The frequency of treatment for bradyarrhythmia
    b. The need for discontinuation of study drug for intolerable side effects

IV. STUDY ENDPOINTS

A. Primary endpoint

The primary endpoint is 30-day all cause mortality.

B. Secondary endpoints

The occurrence of the following events during the initial hospitalization will be considered secondary endpoints:

1. Use of intravenous inotropic therapy and/or vasopressors and/or mechanical support for a failing circulation (IABP, LVAD)
2. Electrical reversion of ventricular fibrillation or sustained ventricular tachycardia
3. Placement of an external or transvenous pacemaker

V. STUDY DESIGN

A. Protocol overview

MAGIC is a multicenter, randomized, double blind, placebo-controlled trial. The projected length of patient enrollment is two years. Eligible patients presenting with a suspected myocardial infarction will be included. If patients are eligible for reperfusion therapy (either thrombolytics or PTCA), they will be included only if they are ≥ 65 years of age and if treatment can be administered within six hours of the onset of symptoms. Patients not eligible for reperfusion therapy will be eligible for randomization irrespective of age, provided treatment can be administered within six hours of the onset of symptoms. Study drug treatment will be administered as a bolus over 15 minutes followed by an infusion for 24 hours. All other treatments should follow standard care for acute MI as outlined in existing publications (such as the ACC/AHA Practice Guidelines) and be at the discretion of the treating physician. (See Figure 2)

VI. PATIENT SELECTION

A. Inclusion criteria

All the following must be present:

1. Ischemic discomfort ≥ 30 minutes in duration.
2. ECG with ST segment elevation ≥ 0.1mV in two or more limb leads, or ≥ 0.2mV in two or more contiguous precordial leads, or new or presumably new left bundle branch block.
3. Able to receive study treatment within six hours of onset of ischemic

discomfort.

4. Written informed consent by patient or legal representative.

B. Exclusion criteria

1. Age < 65 years and patient eligible to receive reperfusion therapy.
2. Unable to give written informed consent, or no immediate relative or legal representative able to give written informed consent.
3. Thrombolytic therapy or primary PTCA for acute MI within the last week other than the current MI.
4. Systolic blood pressure < 90mm Hg despite pressors.
5. Sustained sinus bradycardia < 50/minute prior to randomization.
6. Type II second degree AV block or complete heart block in the absence of a functioning pacemaker.
7. Evidence of severe renal impairment: a. on chronic dialysis; or
   b. creatinine $\geq$ 3mg/dl (265.2 μmol/L).
8. Concomitant participation in another clinical trial involving investigational drugs or devices. ("Investigational" means not approved by the FDA or other regulatory agency for drugs and devices).
9. Patient previously randomized in MAGIC.

VII. STRATIFICATION

For randomization, patients will be stratified by site, and by whether the patient is eligible for reperfusion therapy or not. Stratum I will include patients who are 65 years or older and are eligible for reperfusion therapy. Stratum II will include patients of any age who are not eligible for reperfusion therapy.

VIII. TRANSFER PATIENTS

MAGIC patients who are transferred between institutions at any point during their hospital stay represent a population requiring particular attention. Two principles

should be considered with regard to transfer patients:
1) once a patient is randomized in MAGIC, they will be included in the final analysis according to their initial randomization status, regardless of subsequent treatment ("intention-to-treat" principle); and
2) a patient cannot continue to receive MAGIC study drug once they have been transferred to a non-MAGIC center.

Patients transferred after 24 hours of randomization will be considered discharged from the initial hospitalization. The responsibility for the 30-day follow up will remain with the principal investigator who randomized the patient.

IX. INFORMED CONSENT

No patient may be randomized until written informed consent is obtained. Some patients in the midst of an acute myocardial infarction may not be able to give truly informed consent, either because of their clinical condition or because of prior drug administration. In such cases, a representative legally empowered to act for the patient may give written informed consent. The patient (or legal representative) will be required to sign the informed consent ***before*** randomization. If the patient is not capable of giving informed consent and a legally-empowered representative is not available, the patient will not be randomized. The Informed Consent Form must be approved by the Institution Human Subjects Committee or Review Board of each participating institution.

X. RANDOMIZATION PROCEDURE

Before the patient is randomized, sufficient historical, physical examination and ECG data should be collected to be certain that the inclusion criteria are met and that none of the exclusion criteria are present. Randomization will be accomplished by a telephone call to the Clinical Trial Center (CTC). Confirmation of eligibility and informed consent, and information critical to stratification will be collected at the time of the call.

Randomization will be by the method of randomized permuted blocks with varying block sizes of 4, 6, and 8. Patients and investigators will be blinded to whether they are receiving magnesium or placebo.

XI. ADMINISTRATION OF STUDY DRUG

Each study drug kit will contain a vial with 25.0g (101.0mM) of magnesium sulfate or placebo. Participating institutions will provide sterile solutions of 5% dextrose in water (D_5W) and syringes. If the study drug is to be administered using an infusion pump, a 50 mL infusion bag of 5% dextrose in water will be used for the bolus infusion and a 500 mL bag of 5% dextrose in water will be used for the 24 hour infusion. If the study drug is to be administered using a syringe driver, a single bag of 5% dextrose in water, containing at least 50 mL, will be used for dilution of the study drug in the syringes. For use with an infusion pump, immediately prior to administration, 2.0g (8.0 mM) of magnesium sulfate (or the equivalent volume of placebo) will be placed in the 50mL bag of D_5W, and 17.0g (69.0 mM) of magnesium sulfate (or the equivalent volume of placebo) will be placed in the 500mL bag of D_5W. For use with a syringe driver, immediately prior to administration, 2.0 g (8.0 mM) of magnesium sulfate (or the equivalent volume of placebo) will be diluted in 16 mL of D_5W in a syringe, and 17.0g (69.0 mM) of magnesium sulfate (or equivalent volume of placebo) will be diluted in 14 mL of D_5W in a syringe. The bags for infusion or the syringes will be labeled with the appropriate labels provided in the study drug kit.

The treatment schedule will be the following:

* The small bag or syringe containing a total of 2.0g (8.0 mM) of $MgSO_4$ (or placebo) will be administered over 15 minutes.
* The large bag or syringe containing a total of 17.0g (69.0 mM) of $MgSO_4$ (or placebo) will be administered over 24 hours.

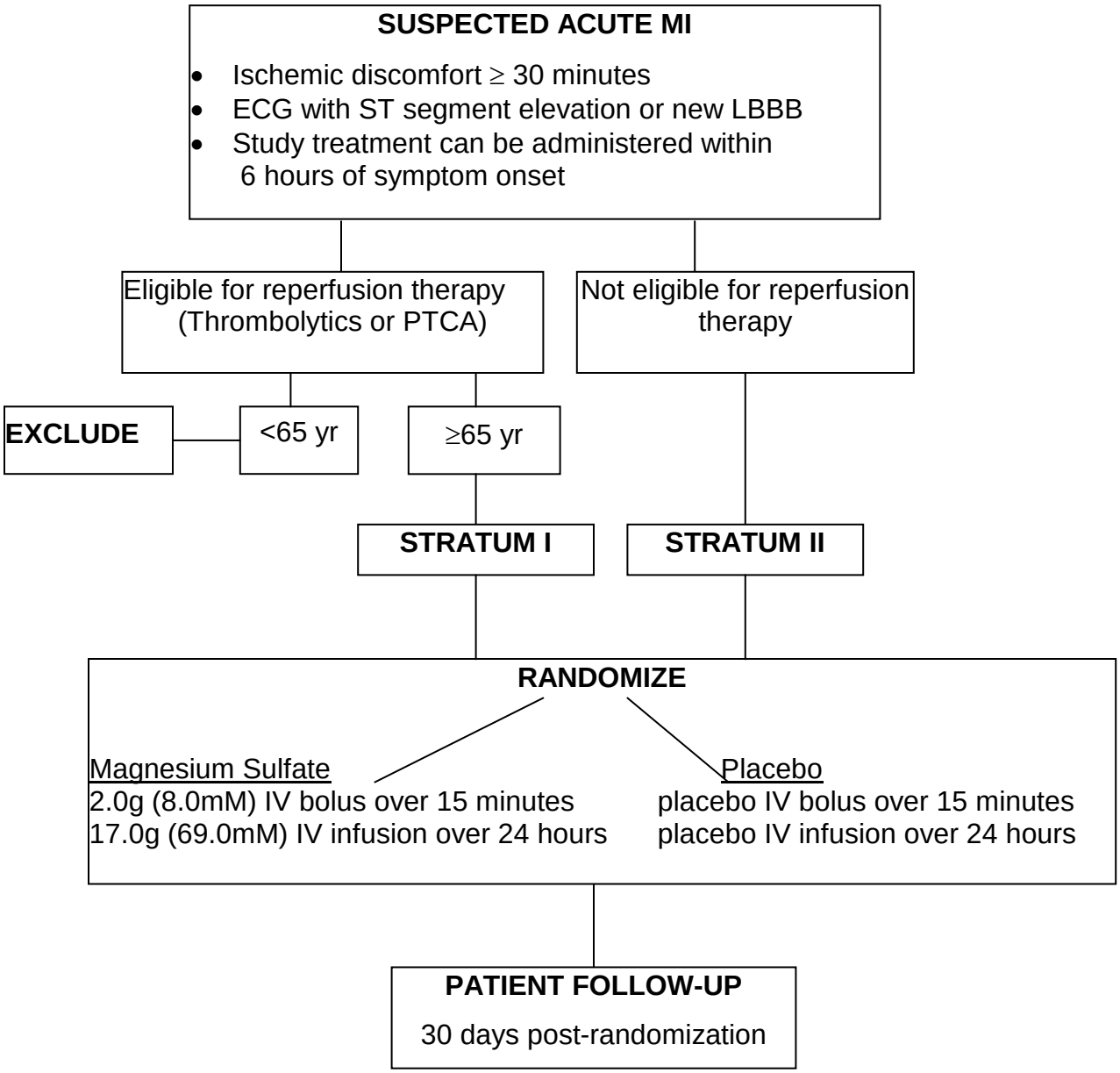
Details of treatment administration are provided in the Manual of Operations and in each study drug kit. For patients undergoing reperfusion, the study drug must be started

before or concurrent with reperfusion therapy. Patients should not be randomized if treatment cannot be started within six hours of the onset of symptoms.

The 24-hour infusion of the study drug should be discontinued if it is found that the patient's creatinine level is $\geq$ 3.0 mg/dl (265.2 μmol/L).

Figure 2

STUDY DESIGN



XI. DATA MANAGEMENT, QUALITY ASSURANCE & MONITORING PROCEDURES

A. Data collection and management

A Manual of Operations will be provided to the investigators as a guide to the operation and management of the study, as well as a technical reference manual. Clinical staff should review the manual and the MAGIC training video prior to the initiation of patient enrollment in order to assure uniformity in patient management and data collection procedures.

The study coordinator at each clinical center will complete the randomization form (Form 01) within one working day of randomization and fax it to the CTC. Originals of all the forms will be kept at the participating investigator's office. All forms will be faxed or sent via the Internet to the CTC upon completion.

B. Monitoring reports

The Clinical Trial Center (CTC) will be responsible for preparing reports to monitor study progress for the Executive Committee, Steering Committee and the Data and Safety Monitoring Board (DSMB). Each type of report will include information on different aspects of the trial.

1. Executive Committee Reports

The recruitment progress of each center and of the whole trial will be updated weekly by the CTC for the Executive Committee. Other reports will be prepared by the CTC as needed by the Executive Committee for the conduct of the study.

2. Steering Committee Reports

To assess the progress of the study, the CTC will prepare routine reports for the Steering Committee. These reports will include, but not be limited to: patient recruitment, patient adherence, quality control and clinical performance data for each center. Special attention will be paid to

recruitment (including recruitment of an appropriate number of women and minorities) during that phase of the study, and to maintaining a high level of adherence. These reports will include summaries of clinical center progress and statistics about patient randomization. No data on endpoints or side effects will be included in these reports.

3. Data and Safety Monitoring Reports

These reports will be prepared at least twice a year and will be tailored to meet the needs of the DSMB. Each report will consist of six major sections: general progress of the study and patient recruitment, endpoints, toxicity and side effects, adherence, data quality, and substudies.

Four weeks prior to the scheduled date of a DSMB meeting, a thoroughly edited data file will be created by the CTC. After the file has been checked, tables and graphs of the data will be produced. The final report will be mailed to members of the DSMB and the NHLBI Project Office at least two weeks prior to the scheduled meeting of the DSMB. Steps will be taken to insure security and confidentiality of the data. These will include: distribution by certified mail and enactment of a return policy on all documents. The tables comparing the treatments with respect to the major outcomes will be updated two days before the meeting so that the DSMB will have the most up-to-date data at the time of the meeting.

C. Quality Assurance

In this large, simple trial, the Quality Assurance (QA) plan must also be streamlined and re-directed so that the burden falls primarily on the CTC, not the clinical centers. The 7-point plan is outlined below.

Drug Packaging

This will be completed in Phase I and quality-controlled by randomly designating "dummy" site numbers. The CTC will identify these, have them shipped to the CTC (to verify shipping procedures) and will chemically test a sample of the kits to ensure correct assignments of $MgSO_4$ and placebo.

On-site Training

Videotape is a cost-effective and pedagogically consistent way to describe the MAGIC protocol to both study coordinators and physicians at the sites. The training video will include: an overview of the MAGIC protocol, patient recruitment, randomization, and treatment administration. The video will cover procedures for which the study coordinators will be responsible, including: form and edit completion, receipt of study drug kits, Manual of Operations (MOO) updates, etc.

Re-creations of expected trial scenarios will be used not only to engage viewers' attention, but also to convey many of the nuances and subtleties involved in proper clinical trial practice and procedures. By serving as role models, the re-creations will further the goal of establishing a standardized, consistent implementation across sites.

Scenes will be directed at the physician (determining eligibility, obtaining informed consent, completing telephone randomization, selecting correct study drug kit) and at the study coordinator (completing data forms, responding to edit queries, maintaining and using the MOO and interfacing with the CTC). A "dummy" randomization must be successfully completed by each site before a real patient is enrolled in the study (this will be automatically verified at the CTC).

Periodically, each site will be asked to list the version dates of all current MOO sections, as well as inventory all numbered memoranda, maintained

chronologically. The list and inventory will be sent to the CTC for verification.

Verification of Patient Eligibility

Apart from eligibility verification during the randomization call, the CTC will check Form 01 for consistency in data.

Verification of Treatment Assignments

The randomization system maintains complete documentation of each call and the system is demonstrably tamper-proof. The key vulnerability is the selection of the correct study drug kit for the randomized patient. The person activating the randomization must verify the kit number by keying it in during the randomization call. The kit number will be re-verified by attaching to Form 01 a peeled-off ID number from the kit label. A patient ID label will in turn be affixed to the kit.

Protocol Compliance/Violation

Apart from verification of eligibility and treatment assignment, the implementation of the IV infusion will also be checked (Form 01) in terms of start time and start date, and reason for termination if early.

To the extent that protocol violations can be detected in real time, they will be monitored and corrective action will be taken with site(s) to reduce/eliminate further violation. Actions will include discussions, and review of the MOO and training video.

Timeliness and Completeness of Data

This will be monitored routinely through the data management system and standard reports that can be run as needed. Sites with late forms or edits or too much missing information will be contacted to identify and correct the problem.

Monitoring Data Accuracy

With direct screen entry and on-line range and logic checks, the data are remarkably error free once entered. Minimal queries to the sites are anticipated.

XIII. STATISTICAL ANALYSES

A. Primary endpoint

The primary endpoint in this trial is 30-day all cause mortality. Treatment effect will be assessed by the difference in the proportion of deaths in the two groups. This hypothesis will be tested with a two-sided Mantel-Haenszel test stratified on eligibility for reperfusion therapy with a type I error of 0.05. An "intention to treat" analysis will be performed.

B. Sample size and power

Sample size was calculated based on detecting a 20 percent reduction in the proportion of patients dying during the first 30 days after a suspected acute MI between the two groups. These calculations were based on a two-sided test of population proportions which will result in a conservative estimate of sample size for the Mantel-Haenszel test. Sample sizes were computed assuming a dilution effect of 11% in the treatment arm. The dilution effect corresponds to the percent of patients who are randomized to the treatment arm and who either:

1. incorrectly report MI symptom onset within 6 hours, or
2. do not receive the magnesium infusion due to refusal or other complications.

This group of patients randomized to the treatment arm is assumed to have the same event rate of the group in the placebo arm.

Table II demonstrates these calculations for a power of 0.90. For a baseline mortality proportion of 10.5 % (based on an estimated 12% mortality among patients $\geq$ 65 years of age receiving reperfusion therapy[2,4-6] , a 9% mortality for

patients not receiving reperfusion therapy and who are randomized within six hours of symptom onset[3,7], and assuming equal numbers in the two strata) with a dilution effect of 11%, a total sample size of approximately 10,500 would be required to detect a 20% reduction in mortality with a two-sided test with a power of 90%. Table III shows the power for varying baseline mortality proportions and dilution effect rates with a fixed sample size of 10,500. Table IV shows the power for detecting percent reductions (due to treatment) of various magnitudes (ranging from 10 to 30 percent) for a fixed sample size (10,500) and baseline proportion of events (0.105). The table suggests that the design has high power to detect a 15-30 percent reduction and moderate to low power to detect a 10-15 percent reduction. This sample size would have high power to detect meaningful differences under a wide range of baseline proportions and dilution effect. Table V shows the sensitivity of the power for varying percentages in the two strata. The table suggests that the design will have high power over a wide range of percentages in the two strata.

Table II

Sample sizes for MAGIC: Based on detecting a 20 percent reduction with a 90 percent power and an 11 percent dilution effect rate.

Prop. Events in Placebo Group	Total Sample Size
0.09	12323
0.105	10405
0.120	8966
0.135	7847
0.15	6952

Table III

Power for detecting a 20 percent reduction with a fixed sample size of 10,500 for varying proportions of events in the placebo arm and varying dilution effect rates.

Prop. Events in Placebo Arm	Power with no dilution effect	Power with 5% dilution effect	Power with 11% dilution effect
0.075	0.865	0.827	0.774
0.09	0.922	0.893	0.849
0.105	0.957	0.937	0.903
0.120	0.977	0.964	0.939
0.135	0.989	0.980	0.963
0.15	0.994	0.989	0.979

Table IV

Power for a fixed sample size of 10,500 and a fixed proportion of events in the placebo arm (10.5%) and varying the detectable difference (%) and dilution effect rates

Detectable difference	Power with no dilution effect	Power with 11% dilution effect
30%	1	0.999
25%	0.997	0.985
20%	0.957	0.903
15%	0.778	0.676
10%	0.435	0.357

Table V

Power for a fixed sample size of 10,500 to detect a 20% reduction with an 11 percent dilution effect and varying the proportions in the two reperfusion strata

Proportion in Stratum II* (Patients not eligible for reperfusion therapy)	Proportion of events in placebo arm	Power
0.50	0.105	0.903
0.40	0.108	0.911
0.30	0.111	0.919
0.20	0.114	0.926
0.15	0.116	0.930

*** Based on a projected 12% and 9% 30-day mortality (in the placebo group) in Stratum I and II, respectively**

C. Subgroup and secondary analyses

Assessing whether there is differential treatment effect in each of the two strata (Stratum I includes patients 65 and older who are eligible for reperfusion therapy, and Stratum II includes patients who are not eligible for reperfusion therapy) is of special interest. Table VI presents the power to detect a 25% reduction in each of the strata under varying proportions of patients in the two strata. The table suggests that there will be moderate power to detect stratum-specific effects as long as more than 30% of patients are in Stratum II. The effect of the method of reperfusion (thrombolysis vs. PTCA), age (<65 and ≥65 on patients not receiving reperfusion therapy), and time (<1hour, 1-3 hours, and 3-6 hours) to treatment will also be analyzed. Additionally, subgroups of particular interest include diabetics, patients with prior MI, whether or not a patient actually receives reperfusion therapy, and patients who have chest pain at the time of the initial study drug infusion. Treatment interactions in each of these subgroups will be examined using logistic regression. Additional statistical testing for the particular subgroup of interest will be made at the 0.05 significance level if the corresponding interaction is significant at the 0.1 level.

Secondary analyses will include a comparison of the frequency of the secondary endpoints (see Section IV, Part B) across treatment groups. In addition, we will compare the frequency of treatment of bradyarrhythmia and the need for discontinuation of study drug for intolerable side effects across treatment arms. Comparisons of the proportions between the two groups will be made using a two-sided Mantel-Haenszel test stratified on eligibility for reperfusion therapy. A significance level of 0.01 will be used for all secondary analyses in order to lower the likelihood of false positive results.

D. Interim analyses

Analyses of the primary endpoint are expected to occur a total of three times in the course of the trial, coincident with meetings of the Data and Safety Monitoring Board (DSMB). While these sample size calculations do not account

for the interim analyses, it is anticipated that the use of conservative interim boundaries, like the O'Brien-Fleming Spending[32,33] function, will decrease the overall power only minimally. For example, with three analyses, one after each third of the data has accumulated, the boundaries 3.71, 2.51, and 1.99 will maintain an overall significance level of 0.05. When the information times are 0.2, 0.6 and 1 (corresponding to 20% of the patients at the first analysis, 60% at the second analysis, and 100% at the final analysis), the boundaries 4.88, 2.67, and 1.98 will maintain an overall level of 0.05. These boundaries will be modified appropriately if the analyses do not occur at exactly these time points. The choice of the final interim analyses methods will be made by the Data and Safety Monitoring Board.

Table VI

Power* to detect a 25% reduction separately in each of the two strata assuming a total sample size of 10,500, 11% dilution effect, and varying proportion of patients in the two strata.

Proportion of patients in Stratum II (Patients not eligible for reperfusion therapy)	Power for Stratum I (Patients ≥ 65 years old and eligible for reperfusion therapy)	Power for Stratum II (Patients not eligible for reperfusion therapy)
0.5	0.88	0.76
0.4	0.93	0.67
0.3	0.96	0.55

*** Based on a projected 12% and 9% 30-day mortality (in the placebo group) in Stratum I and II, respectively.**

XIV. STUDY ORGANIZATION (See Figure 3)

The MAGIC study is sponsored by the National Heart, Lung, and Blood Institute (NHLBI). Day-to-day management of the study will be the responsibility of the NHLBI Project Office, the Clinical Trial Center (CTC), and the Executive Committee.

A. National Heart, Lung, and Blood Institute

The NHLBI is responsible for the overall direction of the trial. The NHLBI will monitor the progress of the study and provide organizational and scientific guidance. The Director of NHLBI has ultimate responsibility for the conduct of MAGIC and serves as the final decision-maker for all major decisions affecting MAGIC. The NHLBI Director appoints the Chair and Members of the Data and Safety Monitoring Board (DSMB).

B. Steering Committee

The voting members of the Steering Committee (SC) will be the Steering Committee Chair, the NHLBI Project Officer, the Clinical Trial Center Principal Investigator, and other investigators appointed by the NHLBI. The SC oversees all aspects of the study. This includes design of the protocol and of the Manual of Operations, monitoring the progress of the trial, analysis of trial results and publication of results. The SC will act upon any special issues that arise. The SC will establish subcommittees, as appropriate, to facilitate the conduct of the study. These will include, but not be limited to, Substudies and Publications. Chairs of these subcommittees will be appointed by the Steering Committee Chair subject to the approval of the NHLBI.

The Executive Committee, composed of the Steering Committee Chair, the NHLBI, and the CTC Principal Investigators, will make recommendations to the SC regarding study conduct, and will provide day-to-day study management.

The SC will meet at least once a year to monitor study progress and to review non-endpoint data. The SC will not have access to endpoint data until the trial is

complete. In any votes of the SC, each member will have a single vote.

C. Clinical Trial Center (CTC)

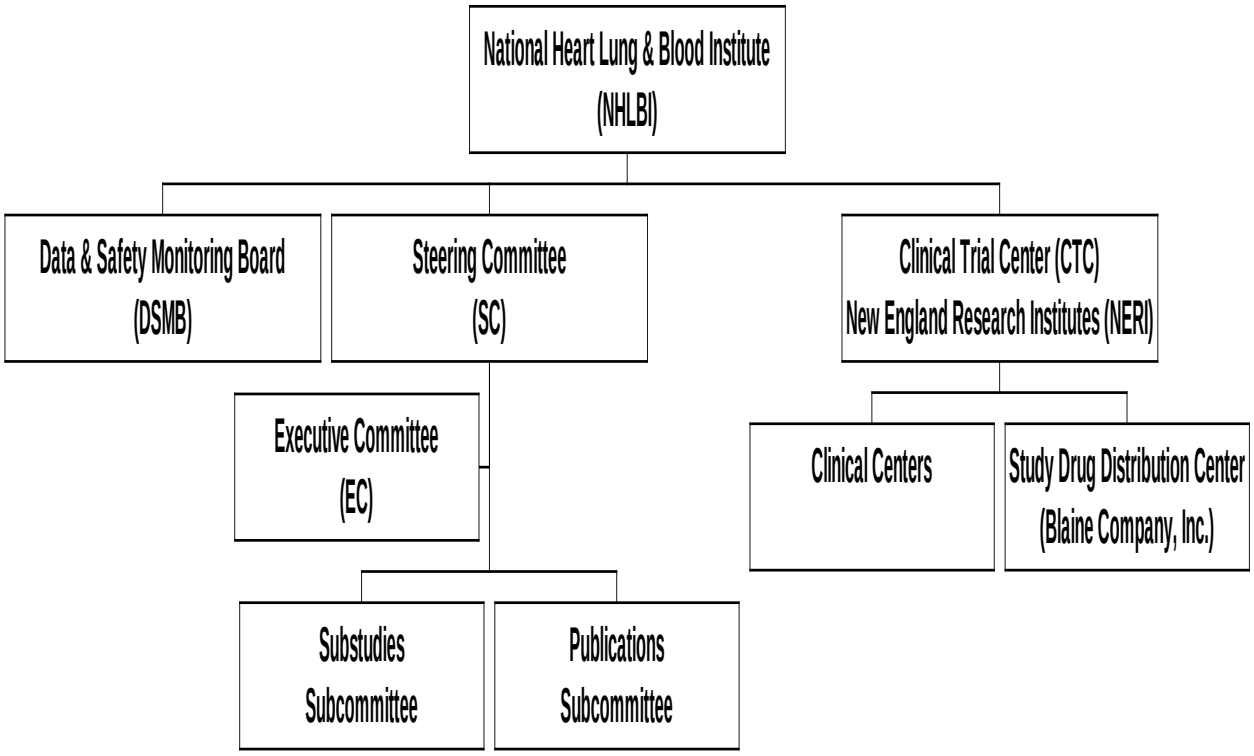
The CTC has the responsibility of contracting the selected clinical sites, in collaboration with the NHLBI. The CTC has primary responsibility for data collection and statistical analysis of the results of the study. In collaboration with the Steering Committee, the CTC develops the Manual of Operations and data collection forms. The CTC is responsible for preparing all reports and minutes of the Executive Committee, Steering Committee, and DSMB.

D. Data and Safety Monitoring Board

A Data and Safety Monitoring Board will be appointed by the Director of the NHLBI to review protocols for the main study and substudies, as well as monitor the conduct of the trial. The DSMB members are independent of the conduct of the study. The DSMB will make recommendations to the Director of the NHLBI about the trial based upon their review of study progress, data, outcomes, toxicity, safety and other confidential data. The DSMB members, as well as the study statisticians and the NHLBI, will have access to endpoint data by treatment group during the conduct of the study. The DSMB will be composed of experts in relevant fields including cardiology, biostatistics, and bioethics. The Steering Committee Chair, the Principal Investigators of the CTC, and the NHLBI Project Officer, are ex-officio members of the DSMB.

Figure 3

Organizational Chart



XV. SUBSTUDIES AND ANCILLARY STUDIES

A. Introduction

Two types of substudies will be defined for MAGIC: ancillary studies and databank studies. Databank studies are based upon data collected as part of the main study, while ancillary studies are those that require data collection beyond those included in the primary protocol. Participation in the substudies is open to all study participants. In order to assure that all substudies are of high scientific merit, the Substudies Committee will review applications for non-protocol studies and make recommendations regarding merit to the Steering Committee.

B. Ancillary studies

An ancillary study uses MAGIC participants in an investigation that is not described in the MAGIC protocol and involves collecting data that are not part of the MAGIC data set. Such studies must be carried out by applicant investigators or in conjunction with MAGIC investigators. In general, any such study will require an independent consent form, IRB approval, DSMB approval, and an independent funding source.

Ancillary studies must be approved by the Steering Committee and the DSMB which will act on the recommendation of the Substudies Committee. All applications for ancillary studies must be submitted in writing to the Substudies Subcommittee. The Subcommittee will judge the scientific merit of the application and make certain that the timing of the resulting publication(s) will not interfere with the main publications of the study.

C. Databank studies

A databank study utilizes data that have been collected as part of the main MAGIC study in order to answer a question different from that posed by the main protocol. It usually involves only data analysis and generally does not require supplemental funding because it uses the resources of the Clinical Trial Center. Such studies require the approval of the Steering Committee which will act on the recommendation of the Substudies Subcommittee. The Subcommittee will judge the scientific merit of the application and assure that reporting of the databank study will not interfere with the main publications of the study.

D. Application review process

The Substudies Subcommittee will review applications for substudies in a timely fashion. If several applications for similar substudies are received, the Substudies Subcommittee will encourage collaboration and joint resubmission. Where irreconcilable differences exist, the Subcommittee will assess the scientific merit of the applications and recommend to the Steering Committee whether one, both or neither of the applications should be approved.

Applications from non-MAGIC investigators will be entertained but will be assigned lower priority than similar applications from MAGIC investigators.

E. Other (non-MAGIC) studies

Simultaneous participation by MAGIC patients in other prospective investigations requires the prior approval of the Steering Committee and is generally to be discouraged. It is recognized that the exigencies of patient care may require that the patient be entered into a compassionate use protocol. If this occurs, the CTC should be notified within 10 days.

F. Data storage and analysis

Any data forms that are faxed to the CTC for data entry will be stored at the CTC and data will be entered into the computer system. The CTC is responsible for

the timely and accurate analysis of data.

XVI. PUBLICATION POLICY

The Publications Subcommittee will review all publications following the guidelines given below and report its recommendations to the Steering Committee.

A. Data analysis and release of results.

The scientific integrity of the project requires that data from all of the MAGIC sites be analyzed study-wide and reported as such. An individual center is expected not to separately report their data. The development of reports of data from individual sites for the determination of institutional variability is the prerogative of the Steering Committee. Additionally, all presentations and publications are expected to protect the integrity of the major study objectives. Endpoint data will not be presented prior to the release of the main study results. Recommendations as to the timing of presentation of endpoint data and the meetings at which they are presented will be given by the Steering Committee.

B. Review process

Each manuscript or abstract must be submitted to the Publications Subcommittee for review of its scientific merit and appropriateness for submission. The Subcommittee may recommend changes to the authors and will submit recommendations to the Steering Committee for a final decision about submission. Each manuscript should also be sent to the NHLBI for review prior to submission.

C. Primary outcome papers, abstracts and presentations

The primary outcome papers of MAGIC are defined as those that present outcome data for the MAGIC patient cohort as a group (such as mortality reduction by magnesium, if present). The determination of whether or not a particular analysis represents a primary outcome will be made by the Steering

Committee based on a recommendation from the Publications Subcommittee.

Authorship on the baseline and primary outcome papers will be "The MAGIC Investigators." For such manuscripts, there will be an appendix containing the names of all participants in the study and their organizational affiliation.

Papers and abstracts that are not primary outcome papers will have named authors based upon involvement and ending with the phrase "for the MAGIC Investigators." The same appendix will be appended to non-primary outcome manuscripts as for primary outcome papers. All publications must be approved by the Steering Committee which may delegate this authority to the Publications Subcommittee.

XVII. CLOSEOUT PROCEDURES

MAGIC may terminate at the planned target of 30 days after the last participant has been randomized or at an earlier date if circumstances warrant. In either event, the objectives of the closeout phase are:

1. Evaluate as fully as possible the data to permit assessment of the effect of magnesium administration in all cause 30-day mortality.

2. To fulfill ethical obligations to trial participants.

3. To exploit the scientific value of study data as fully as possible.

Closeout procedures, including recommendations for further patient care, will be developed by the Steering Committee. Regardless of the timing and circumstances of the end of the study, closeout will proceed in two stages: An interim period for analysis and documentation of study results, and a final reporting of the main study results.

A. Interim

About 3 to 4 months will be needed to complete data collection and to prepare a manuscript for submission to an appropriate journal.

B. Reporting of study results

The study will be released to the participating physicians, referring physicians, patients and to the general medical community.

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