A Multi-Centre Cluster, Cross-Over, Pilot Study Comparing the Safety and Efficacy of Magnesium Loading Followed by Infusion, with Magnesium Intermittent Boluses, in Intensive Care Unit Patients Requiring Vasoactive Pharmacological Support and Invasive Mechanical Ventilation

Statistical Analysis Plan

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INTRODUCTION

Atrial fibrillation is a frequent complication in critically ill patients, with incidence rates ranging from 4.1% to 46%, particularly among those with sepsis or undergoing cardiac surgery.[1,2] It is associated with worse outcomes, including increased mortality, morbidity, and length of stay.[2,3] Although treatments like beta-blockers, amiodarone, and digoxin are commonly used, their side effects, especially in critically ill patients, highlight the need for safer alternatives.[4] Magnesium has emerged as a potential agent, with evidence from cardiac surgery studies suggesting it may reduce atrial fibrillation incidence and duration.[5,6] Magnesium plays a vital physiological role, particularly in maintaining electrolyte balance and stabilising cardiac membranes, with ionised magnesium (iMg) being the biologically active form.[7] However, standard practice relies on total magnesium (tMg) levels, which may not reliably reflect intracellular stores, especially during critical illness.[7]

Hypomagnesemia is common in intensive care unit (ICU) patients, with a prevalence of up to 61%, and is linked to poor outcomes including increased arrhythmias, prolonged ventilation, and higher mortality.[7,8] Despite its clinical relevance, intracellular magnesium remains difficult to measure accurately, prompting calls to monitor iMg and its ratio to tMg as better indicators for magnesium status and atrial fibrillation risk.[7,8] There is still uncertainty regarding the optimal magnesium dose, target levels for iMg and tMg, and ideal method of administration. Recent studies in post-cardiac surgery populations suggest that mild hypermagnesemia (1.5–2.0 mmol/L) is safe and may reduce new-onset atrial fibrillation.[6,9,10]

The present study outlines the protocol and statistical analysis plan for a cluster cross-over pilot randomised clinical trial comparing the effect of continuous versus intermittent magnesium replacement on the duration of newly diagnosed atrial fibrillation in patients receiving mechanical ventilation and vasoactive support. Recruitment for the trial has now been completed but data collection is ongoing, and no data analysis has yet been undertaken. This trial is registered with ANZCTR (ACTRN12622001076763).

METHODS

Study design

National open-label, two centre, cluster cross-over, registry-embedded randomised clinical trial comparing two approaches for magnesium replacement among adult patients requiring mechanical ventilation and vasoactive support. The protocol was approved by the Austin Health Human Research Ethics Committee (HREC), and informed consent was waived or an opt out process was followed according to local jurisdictions. No interim analyses were planned.

The cluster cross-over design allocates the entire ICU rather than individual patients, with each ICU defining a cluster, and each ICU crossing over to use both strategies being tested by the end of the study. This design should help in minimising contamination and create a situation that would reflect daily practice in a realistic way. Furthermore, the registry-embedded design facilitates data collection, as most data will be obtained from existing data sources (CORE Outcome Measurement and Outcome Tool [COMET]).

Study population

Patients aged 18 years or older requiring invasive mechanical ventilation and vasoactive support (defined as the need of a continuous infusion of a vasopressor) at any time during ICU admission were eligible for inclusion in the study. Patients with known allergy to magnesium sulphate, chronic atrial fibrillation, post-cardiac surgery, severe chronic kidney disease (eGFR< 30 mL/min/m^2), severe oliguria (< 0.5 mL/kg/h for 12 hours), a serum total magnesium < 0.4 mmol/L, or pre-eclampsia, eclampsia or postpartum hypertension, were excluded from the trial. Patients who were admitted and

fulfilled eligibility criteria on more than one occasion had only their first admission included for analysis.

Randomisation and masking

The study compared two approaches for magnesium replacement among adults requiring mechanical ventilation and vasoactive support. One approach was to use a continuous infusion of magnesium and the other was to use intermittent boluses of magnesium at the discretion of the treating team. Each ICU used one approach for a 6-month treatment period and then switched to the alternative approach for the next 6 months. The participating units were randomized to the order of treatment (intermittent - continuous or continuous - intermittent). Clinicians, and investigators were aware of group assignments.

Intervention

This unblinded trial employed an open-label design for treatment administration. Patients in the 'Intermittent' group (usual care) received intravenous boluses of 10–20 mmol of magnesium at the discretion of the treating clinicians, with the goal of maintaining a total serum magnesium level above 0.7 mmol/L. In contrast, patients in the 'Continuous' group (intervention) received a 10 mmol loading dose over one hour if their total magnesium level was below 1.5 mmol/L, followed by a continuous infusion at 1.5–3.0 mmol/h. The target magnesium levels for this group were either an ionised magnesium concentration between 0.9–1.3 mmol/L or a total serum magnesium concentration of 1.5–2.0 mmol/L. The continuous infusion was maintained for up to four days or until ICU discharge, whichever occurred first (**Figure 1**).

In both groups, treatment could be discontinued if the clinical team opted out of the assigned strategy, determined that alternative magnesium levels were needed, or if specific safety criteria were met, such as a urine output < 0.5 mL/kg/h for 12 consecutive hours, or the cessation of vasoactive drugs and mechanical ventilation. Daily monitoring included both total and ionised serum magnesium levels to guide therapy and ensure safety. Patients who remained in the ICU through the crossover period continued to receive their originally assigned treatment. No washout occurred between crossover periods.

Data collection

Baseline demographic data, illness severity, and patient outcomes are being sourced from the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Adult Patient Database (ANZICS-APD), a repository of routinely collected data maintained by trained ICU personnel for quality assurance purposes. This ensures consistency and reliability in the core clinical variables used for analysis.

In addition, individual patient-level data on laboratory parameters, including total serum magnesium, urea, creatinine, eGFR, calcium, phosphate, albumin, total protein, and liver function tests, will be extracted from electronic medical records (EMR). All point-of-care test results, such as serum ionised magnesium, ionised calcium, and the ionised-to-total magnesium ratio, will also be collected. Data on heart rhythm, heart rate, blood pressure, and atrial fibrillation episodes will be obtained from standard ICU observation charts and continuous electrocardiogram (ECG) monitoring systems via the EMR. Antiarrhythmic or rate control medications, such as Amiodarone, Digoxin and

beta-blockers, will be recorded. Details related to study treatments, including total magnesium dose administered, infusion duration, and concurrent vasopressor use, will be retrieved by trained investigators. Random audits of data entries are being performed to ensure accuracy and data integrity.

Study outcomes

Primary outcome

The primary outcome is the duration of new-onset atrial fibrillation within the first four days following trial inclusion or until ICU discharge, whichever occurs first. Duration of new-onset atrial fibrillation is defined as the time elapsed from the initial onset of atrial fibrillation to the documented return to sinus rhythm. Atrial fibrillation was defined according to standard criteria as an irregularly irregular rhythm with no distinct P waves on electrocardiogram, lasting at least 30 seconds.[11]

Secondary outcomes

Secondary outcomes include:

- Incidence of atrial fibrillation;
- Incidence of atrial fibrillation with rapid ventricular response (defined as a heart rate > 130 bpm);
- Hours alive and free of atrial fibrillation at day four (defined as the number of hours from day one to day four when the patient is alive and without atrial fibrillation, with patients who died assigned zero hours);
- Use of other anti-arrhythmic agents including amiodarone, digoxin or beta-blockers;
- Duration of mechanical ventilation;

- Duration of vasopressor infusion;
- Clinical complications including delirium, stroke, and pneumonia (as coded at ICU discharge using ICD-10 codes);
- Atrial fibrillation at ICU discharge;
- ICU-free days at day 28 (defined as the number of days from day 1 to day 28 when the patient is alive and outside the ICU, with patients who died or were at the ICU after 28 days assigned zero ICU–free days);
- Hospital-free days at day 28 (defined as the number of days from day 1 to day 28 when the patient is alive and outside the hospital, with patients who died or were at the hospital after 28 days assigned zero hospital–free days);
- ICU mortality;
- Hospital mortality;
- 28-day in-hospital mortality.

Adverse event reporting

Magnesium administration may cause side effects such as transient hypotension, reduced reflexes, muscle weakness, and flushing, effects that are more commonly observed with bolus dosing. While these adverse effects are generally well tolerated in critically ill patients, the primary safety concern is the occurrence of significant adverse events that necessitate discontinuation of the study drug. All such events leading to treatment cessation will be recorded and monitored throughout the trial.

Sample size

These two methods of magnesium replacement have not previously been compared in clinical trials involving ICU patients receiving mechanical ventilation and vasoactive support. This study is designed as a pilot to assess the feasibility of conducting a larger trial comparing these two strategies. It also aims to establish the primary outcome, duration of new-onset atrial fibrillation by day four, in a population of non-cardiac surgery patients requiring vasoactive therapy. In addition, the study will generate baseline data for key secondary outcomes to inform the design and planning of future trials.

As this is a cluster cross-over trial involving two centres, the method of magnesium administration will be implemented in predefined 6-month periods at each hospital, alternating between the two treatment strategies. Rather than targeting a specific number of enrolled patients, all eligible patients admitted during each intervention period will be included. Based on historical admission data, it is anticipated that approximately 300 patients meeting inclusion criteria (mechanically ventilated and receiving vasopressors or inotropic support) will be enrolled across both sites over the study duration.

Although formal power calculations in cluster cross-over designs must account for within-cluster correlation and period effects, provisional estimates based on prior ICU studies suggest that at least 20 patients in each treatment group are expected to develop new-onset atrial fibrillation. Under individual-level assumptions, this would provide >90% power to detect a reduction in atrial fibrillation duration from 8 to 5 hours, assuming a standard deviation of 2 hours. These estimates will be refined in future studies using appropriate methods for cluster cross-over trials.

Statistical analyses

All statistical analyses will be conducted on an intention-to-treat basis, with patients analysed according to their assigned treatment arms, unless otherwise indicated (**Figure 2**). No or minimal losses to follow–up for the primary and secondary outcomes are anticipated. Complete–case analysis will be carried out for all the outcomes. However, if more than 5% of missing data were found for the primary outcome, a sensitivity analysis using multiple imputations and estimating–equation methods will be carried out.

Hypothesis tests will be two–sided with a significance level of 0.05. Analyses will be performed using the R v.4.3.3 (R Core Team, 2016, Vienna, Austria) program.

Baseline characteristics

A description of the baseline characteristics of the trial participants will be presented by treatment group and by period (**Table 1**). Discrete variables will be summarized as numbers (%). Percentages will be calculated according to the number of trial participants for whom data are available. Where values are missing, the denominator will be stated in the table and no assumptions or imputations will be made. Continuous variables will be summarized by either means and standard deviations (SD) or medians and interquartile ranges (IQR), according to the observed distribution of the variable.

Treatment characteristics

Treatment characteristics including total dose of magnesium will be reported according to the **Table 3**, and in the figures proposed below. Absolute differences between the groups with the respective 95% confidence interval will be calculated and presented.

Proposed additional figures

Figure X – Total and Ionised Magnesium Levels Over Time.

A two-panel figure showing the total and the ionised magnesium level until day 4 in each group. Data will be presented as mean and 95% confidence interval.

General model for outcomes

All analyses for outcomes will use individual patient-level data, and all models will consider the ICU as the cluster unit (random effect), and will include as fixed effects the treatment group (continuous vs. intermittent). Despite the small number of clusters, random intercepts for ICU will be included to account for clustering at the ICU level, acknowledging the limited degrees of freedom for between-cluster variance estimation. Since only two clusters were included, the order of administration of the treatments (1^{st} or 2^{nd} period) will be considered in a sensitivity analysis only, to account for the order and secular time effect. This was chosen because due to the small number of clusters there may not be sufficient data to differentiate the order effect from the treatment effect. In addition, the intra-cluster correlation coefficient, the intra-period correlation coefficient, and the intra-cluster intra-period correlation coefficient will be calculated.

Primary outcome

The primary outcome, defined as the duration (in hours) of new-onset atrial fibrillation within the first four days following trial inclusion or until ICU discharge (whichever occurred first), will be analysed only among patients who developed atrial fibrillation using a mixed-effects quantile regression model with $\tau = 0.50$ (median regression) to estimate the effect of continuous magnesium infusion compared with intermittent replacement, while accounting for clustering at the ICU level. Patients who died before atrial fibrillation resolution will be assigned

the maximum follow-up duration (96 hours) as their atrial fibrillation duration, assuming persistence of atrial fibrillation until death. Results will be reported as median difference with a 95% confidence interval (**Table 4**).

To support interpretation, a confidence distribution for the primary outcome using a normal approximation on the estimated median difference will be calculated.[13] The confidence distribution will be computed to provide the frequentist probability that the median difference is lower than 0. In addition, the confidence distribution will be reported in a plot.[13]

Secondary outcomes

Binary secondary outcomes will be modelled considering a mixed-effect generalized linear model with binomial distribution and presented as odds ratio and 95% confidence interval. Continuous variables will be analysed using the same model implemented for the primary outcome and reported as median difference and 95% confidence intervals. Hours alive and free of atrial fibrillation at day four, ICU- and hospital-free days will be analysed using a mixed-effect cumulative logistic regression model and reported as common odds ratio and 95% confidence intervals. The 28-day in-hospital mortality will be compared using (shared-frailty) Cox proportional hazard models, and presented as hazard ratio with 95% confidence interval, and in Kaplan-Meier curves. The proportional hazard assumption will be assessed using Schoenfeld residuals. (**Table 4**).

Proposed additional figures

Figure X - Hours Alive and Free of Atrial Fibrillation at Day Four According to Allocation Group

A two-panel figure with a cumulative distribution plot sowing the cumulative fraction of patients in each hour alive and free of atrial fibrillation at day four. The

spike at 0 represents patients who died or who had atrial fibrillation duration equal or longer than four days, and the right part of the graph the duration of atrial fibrillation. The line most at right represents a shorter duration of atrial fibrillation in survivors (more days alive and free of atrial fibrillation). The second panel will show a bar plot representing the percentage of patients in each category of the hours alive and free of atrial fibrillation at day four.

Figure X - 28-Day In-Hospital Mortality

A Kaplan-Meier curve.

Subgroup analysis

The interaction between the allocation group and the following pre-specified subgroups will be assessed in the model described above for the primary outcome:

- Age (< 65 vs. ≥ 65 years);
- Sex (male vs. female);
- Baseline total serum magnesium (< median vs. ≥ median);
- Baseline ionised serum magnesium (< median vs. ≥ median);
- APACHE score (≤ median vs. > median);
- Vasoactive support level (single agent vs. two or more agents).

Sensitivity analysis

An additional analysis for the primary outcome will be carried out adjusting for APACHE and for any other imbalanced variable ($p < 0.01$) at baseline. An additional model for the primary outcome will be carried out including the order of administration of the treatments (1^{st} or 2^{nd} period) as fixed effect, to account for the order and secular time effect. Finally, to account for the occurrence of death before atrial fibrillation resolution, duration of atrial fibrillation will be compared

considering a Fine-Gray competing risk model with death before the event as a competing risk, and presented in cumulative incidence plots and with subdistribution hazard ratio and 95% confidence interval.

Data Sharing Statement

De-identified data will be made available on reasonable request to the corresponding author.

CONCLUSION

This Statistical Analysis Plan details pre-specified methods that will be used to evaluate the safety and comparative effectiveness of continuous versus intermittent magnesium replacement in critically ill adults requiring vasoactive support and invasive mechanical ventilation. The findings of this trial will inform the feasibility and design of a definitive multicentre study aimed at optimising magnesium therapy to improve clinical outcomes in the intensive care setting.

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Table 1 – Baseline Characteristics of the Included Patients

	Continuous (*n* = XXX)	Intermittent (*n* = XXX)
Age, years		
Gender - no. (%)		
Male		
Female		
Weight, kilograms		
Body mass index, kg/m^2		
APACHE II[a]		
Type of admission - no. (%)		
Medical		
Elective surgery		
Emergency surgery		
Presentation at ICU admission - no. (%)		
Acute respiratory failure		
Cardiac arrest		
Sepsis		
Shock		
ICU source of admission - no. (%)		
Emergency department		
Operating room		
Ward		
Other hospital		
Other ICU		
Other		
Admission diagnosis - no. (%)		
Gastrointestinal		
Respiratory		
Trauma		
Cardiovascular		
Neurological		
Sepsis		
Musculoskeletal		
Renal genitourinary		
Gynecological		
Metabolic		
Hematological		
Co-existing disorders - no. (%)		
Chronic respiratory disease		
Chronic cardiovascular disease		
Chronic kidney disease		
Liver dysfunction		
Immunosuppression		
Metastatic cancer		

Table 1 – Baseline Characteristics of the Included Patients

	Continuous (*n* = XXX)	Intermittent (*n* = XXX)
Vital signs and laboratory tests in the first 24 hours		
Lowest mean arterial pressure, mmHg		
Highest heart rate, bpm		
Urine output, millilitres		
pH		
PaO_2 / FiO_2		
Highest creatinine, µmol/L		
Creatinine < 150 µmol/L		
eGFR, mL/min/1.73m2		
Total serum magnesium, mmol/L		
Ionized serum magnesium, mmol/L		
Albumin, g/L		
Urea, mmol/L		
Ionised Calcium, mmol/L		
Lactate, mmol/L		

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding. Denominators are shown when the overall sample size was not available.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; FiO2, fraction of inspired oxygen; ICU, intensive care unit; PaO2, partial pressure of arterial oxygen.

[a] APACHE II score ranges from 0 to 71, with higher scores indicating more severe disease and a higher risk of death, e.g., an APACHE II score of 24 means 40% probability of mortality in a medical patient admitted due to a respiratory condition.

Table 2 – Baseline Characteristics of the Included Patients

	Period 1 Intermittent (*n* =)	Period 2 Continuous (*n* =)	Period 1 Continuous (*n* =)	Period 2 Intermittent (*n* =)
Age, years				
Gender - no. (%)				
Male				
Female				
Weight, kilograms				
Body mass index, kg/m^2				
APACHE II[a]				
Type of admission - no. (%)				
Medical				
Elective surgery				
Emergency surgery				
Presentation at ICU admission - no. (%)				
Acute respiratory failure				
Cardiac arrest				
Sepsis				
Shock				
ICU source of admission - no. (%)				
Emergency department				
Operating room				
Ward				
Other hospital				
Other ICU				
Other				
Admission diagnosis - no. (%)				
Gastrointestinal				
Respiratory				
Trauma				
Cardiovascular				
Neurological				
Sepsis				
Musculoskeletal				
Renal genitourinary				
Gynecological				
Metabolic				
Hematological				
Co-existing disorders - no. (%)				
Chronic respiratory disease				
Chronic cardiovascular disease				
Chronic kidney disease				
Liver dysfunction				
Immunosuppression				

Table 2 – Baseline Characteristics of the Included Patients

	Period 1 Intermittent (*n* =)	Period 2 Continuous (*n* =)	Period 1 Continuous (*n* =)	Period 2 Intermittent (*n* =)
Metastatic cancer				
Vital signs and laboratory tests in the first 24 hours				
Lowest mean arterial pressure, mmHg				
Highest heart rate, bpm				
Urine output, millilitres				
pH				
PaO_2 / FiO_2				
Highest creatinine, µmol/L				
Creatinine < 150 µmol/L				
eGFR, mL/min/1.73m2				
Total serum magnesium, mmol/L				
Ionized serum magnesium, mmol/L				
Albumin, g/L				
Urea, mmol/L				
Ionised Calcium, mmol/L				
Lactate, mmol/L				

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding. Denominators are shown when the overall sample size was not available.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; FiO2, fraction of inspired oxygen; ICU, intensive care unit; PaO2, partial pressure of arterial oxygen.

[a] APACHE II score ranges from 0 to 71, with higher scores indicating more severe disease and a higher risk of death, e.g., an APACHE II score of 24 means 40% probability of mortality in a medical patient admitted due to a respiratory condition.

Table 3 – Treatment Characteristics

	Continuous (*n* = XXX)	Intermittent (*n* = XXX)	Absolute Difference (95% CI)	*p* value
Magnesium level at the start of the infusion, mmol/L				
Total				
Ionized				
Duration of infusion, hours				
Total amount of magnesium given, mmol				

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding. Denominators are shown when the overall sample size was not available.

Table 4 - Clinical Outcomes According to the Groups

	Continuous (*n* = XXX)	Intermittent (*n* = XXX)	Effect Estimate (95% CI)	*p* value
Primary outcome				
Duration of new-onset atrial fibrillation at day four Mean ± standard deviation			Median Difference	
Secondary outcomes				
Incidence of atrial fibrillation – no. (%)			Odds ratio	
Incidence of atrial fibrillation with rapid ventricular response* – no. (%)			Odds ratio	
Hours alive and free of atrial fibrillation at day four**			Odds ratio	
Use of other anti-arrhythmic agents[a] – no. (%)			Odds ratio	
Duration of mechanical ventilation, hours			Median Difference	
Duration of vasopressor infusion, hours			Median Difference	
Clinical complications – no. (%)			Odds ratio	
Delirium			Odds ratio	
Stroke			Odds ratio	
Pneumonia			Odds ratio	
Atrial fibrillation at ICU discharge – no. (%)				
ICU-free days at day 28[b]			Median Difference	
Hospital-free days at day 28[b]			Median Difference	
ICU mortality – no. (%)			Odds ratio	
Hospital mortality – no. (%)			Odds ratio	
28-day in-hospital mortality – no. (%)			Hazard ratio	

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding. Denominators are shown when the overall sample size was not available.

* Defined as a heart rate > 130 bpm.

** Defined as the number of hours from day 1 to day 4 when the patient is alive and without atrial fibrillation, with patients who died assigned zero hours.

[a] Including amiodarone, digoxin or beta-blockers.

[b] Defined as the number of days from day 1 to day 28 when the patient is alive and outside the ICU/hospital, with patients who died or were at the ICU/hospital after 28 days assigned zero free days

MODIFICATIONS FROM THE ORIGINAL ANALYSIS PLAN

ANALYSIS	ORIGINAL PLAN	UPDATE IN THE SAP (Closed in May 05, 2025)
Duration of atrial fibrillation from onset to return to sinus rhythm	Duration of new-onset atrial fibrillation within the first four days following trial inclusion or until ICU discharge, whichever occurs first	Complete definition
Incidence of fast atrial fibrillation	Incidence of atrial fibrillation with rapid ventricular response (defined as a heart rate > 130 bpm)	Complete definition
Day alive and free of atrial fibrillation	Hours alive and free of atrial fibrillation at day four (defined as the number of days from day 1 to day 4 when the patient is alive and without atrial fibrillation, with patients who died assigned zero hours)	Complete definition
Use of other anti-arrhythmic agents including amiodarone or digoxin	Use of other anti-arrhythmic agents including amiodarone, digoxin or beta-blockers	Complete definition
Duration of vasopressor and inotrope infusions	Duration of vasopressor infusion	Inotropes removed from the definition
---	Atrial fibrillation at ICU discharge	New outcome included
ICU-free days at 28 days	ICU-free days at day 28 (defined as the number of days from day 1 to day 28 when the patient is alive and outside the ICU, with patients who died or were at the ICU after 28 days assigned zero ICU–free days)	Complete definition
Hospital-free days at 28 days	Hospital-free days at day 28 (defined as the number of days from day 1 to day 28 when the patient is alive and outside the hospital, with patients who died or were at the hospital after 28 days assigned zero hospital–free days)	Complete definition

Figure 1 – Algorithm of Infusion in the Continuous Replacement Group

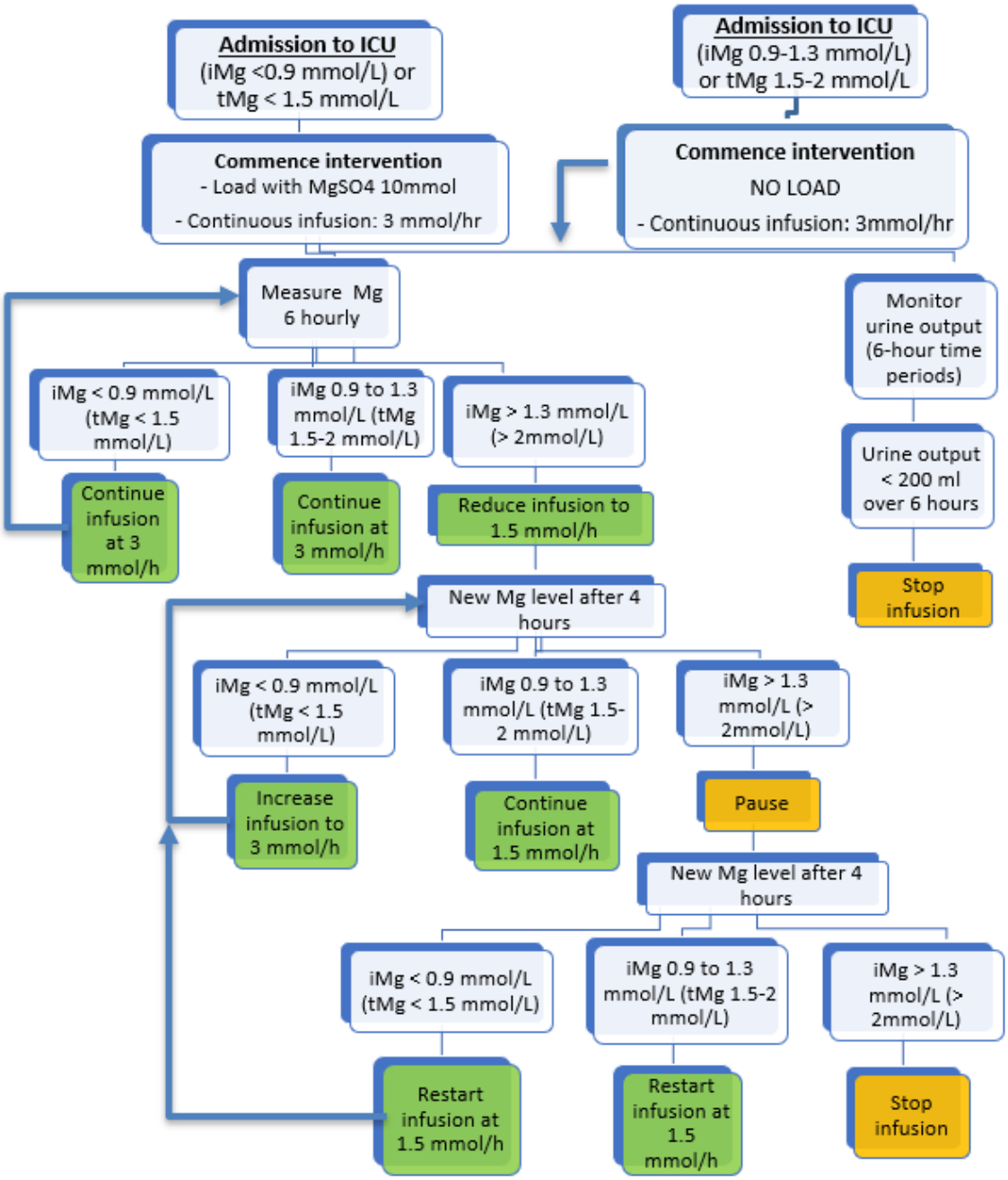

Figure 2 – Flowchart of Inclusion