A prospective randomised controlled trial of the effect of Magnesium Sulphate administration on Red Cell Transketolase Activity in Alcohol dependent patients at risk of Wernicke Korsakoff Syndrome treated with Thiamine

Running title:	**Effect of Magnesium and Thiamine on red cell transketolase activity**
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Funder:	**Supported by A&E and Biochemistry departments of NHS Greater Glasgow and Clyde**

Amendment number	Date	Protocol version

This study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006) and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended).

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Funding Body

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PROTOCOL APPROVAL

Effect of Magnesium and Thiamine on red cell transketolase activity

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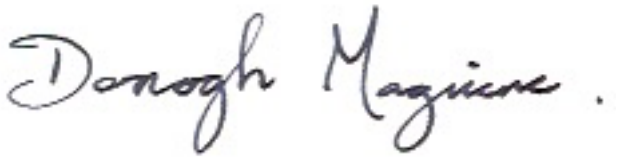

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ABBREVIATIONS

A&E	Accident and Emergency
AE	Adverse event
CRF	Case Report Form
ED	Emergency Department
FAST	Fast Alcohol Screening Test
GMAWS	Glasgow Modified Alcohol Withdrawal Scale
GRI	Glasgow Royal Infirmary
IV	Intravenous
REC	Research Ethics Committee
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
TKA	Transketolase
WE	Wernicke's Encephalopathy

STUDY SYNOPSIS

Title of Study:	**Effect of Magnesium and Thiamine on red cell transketolase activity**
Study Centre:	Glasgow Royal Infirmary
Duration of Study:	12 months
Primary Objective:	Does magnesium administration enhance the biochemical response to thiamine as measured by the activity of the enzyme transketolase in red blood cells?
Secondary Objective:	What is the effect of the administration of thiamine alone, Magnesium alone, or both together on - Plasma lactate concentrations - Biomarkers of ageing
Primary Endpoint:	Change in erythrocyte transketolase activity after treatment with - Thiamine - Magnesium - Thiamine plus magnesium
Rationale:	Chronic alcoholics have a 30-80% incidence of thiamine deficiency causing Wernicke's Encephalopathy (WE). Intravenous (IV) thiamine replacement is standard practice in the treatment of alcoholic patients presenting to the Accident & Emergency (A&E) department, however routine co-supplementation with magnesium (administered IV as magnesium sulphate), a co-factor for thiamine in some metabolic processes, e. g. on the activity of the enzyme transketolase in red blood cells, is not routine practice in the treatment of these patients. Without correction of concomitant magnesium deficiency there may be impaired utilisation of thiamine resulting in a failure to treat WE. This study is designed to determine if administration of Magnesium to alcoholic patients affects red cell transketolasae by itself, or only acts to increase the effect of thiamine on the activity of this enzyme.
Methodology:	Open label, randomised controlled study
Sample Size:	120
Screening:	Confirmation of chronic alcoholism (FAST questionnaire. GMAWS score)
Registration/Randomisation:	Randomisation will be performed using individually numbered opaque envelopes.
Main Inclusion Criteria:	• Chronic alcohol dependence
Main Exclusion Criteria:	• Known chronic renal failure
Product, Dose, Modes of Administration:	Participants will be randomised to: • **Arm 1:**Thiamine • **Arm 2:** Thiamine and magnesium sulphate • **Arm 3:** Magnesium sulphate with delayed thiamine where thiamine will be administered as Pabrinex.
Duration of Treatment:	Each infusion will be administered over 30 minutes
Statistical Analysis:	A three group study was designed to detect a minimum biochemically significant difference of 0.16 in the change from baseline between the groups, with 80% power and a 5% significance level. total sample size = 120. Methodology: One way ANOVA

1. INTRODUCTION

1.1 Background

Alcohol related conditions account for up to 40% of weekday Emergency Department attendances.[1] [II] Socioeconomic deprivation has a well-proven association with rates of alcoholism in the community.[2] Glasgow Royal Infirmary serves the north and east of Glasgow, parts of which have been designated by the WHO to be among the most deprived areas in Europe.[2]

Between 30-80% of chronic alcoholics have thiamine deficiency. The incidence of Korsakoff's psychosis has been noted to be steadily increasing in the East End of Glasgow since 1990.[3] Wernicke-Korsakoff Psychosis has also been shown to be related to Thiamine deficiency. Magnesium (Mg^{2+}) is known to be an essential cofactor for Thiamine, though its effect on the enzyme transketolase, in the Pentose Phosphate Shunt and as such is advocated by core Emergency Medicine texts in the treatment of alcoholic or malnourished patients.[4]

The aim of this project is to further clarify the effect of concurrent magnesium supplementation with thiamine administration on Red Cell Transketolase (TKA) Activity in a cohort of alcoholic patients admitted through ED. Patients will be determined to be alcohol dependant from history (FAST questionnaire) or in alcohol withdrawal as determined by the GMAWS scale (appendix).

1.2 Rationale

Thiamine and Magnesium in the Alcohol Withdrawal Patient

Chronic alcoholics have a 30-80% incidence of clinical or biochemical signs of thiamine deficiency.[5] Wernicke's Encephalopathy (WE) is not a rare disorder. Autopsy studies have revealed a prevalence of 2% in western society among the general population.[5] Untreated WE has a mortality rate of 20% and a progression along its clinical spectrum to Korsakoff psychosis of 85%.[5]

Parenteral thiamine replacement is standard practice in the treatment of alcoholic patients presenting to the A&E department. However despite the fact that routine co-supplementation with magnesium sulphate is practiced by many doctor's in the treatment of these patients

(authors own experience and peer consensus), the underlying mechanism and efficacy is not yet fully understood.

Low total body magnesium results from the direct effect of alcohol on the nephron, which causes urinary Mg^{2+} wastage. Malnutrition and poor dietary intake of magnesium also contribute to poor levels of total body magnesium.[8]

Clinician's often fail to recognise the presence of magnesium deficiency in their patients as they rely on serum values of magnesium. The measureable serum value reflects only 0.15% of total body magnesium, as magnesium is predominantly intracellular and protein bound. Serum values do not drop until critical deficiency exists. Without correction of baseline magnesium deficiency there may be impaired utilisation of thiamine.[10]

The Cochrane review states that there is insufficient evidence as to the duration of treatment and dosages of Thiamine required for the treatment of Wernicke-Korsakoff Syndrome, while acknowledging that thiamine utilization in patients experiencing alcohol withdrawal is probably influenced by Mg^{2+} status.[9, 11]

Current evidence consists mainly of case reports and clinical observations. Given the weight of biochemical evidence available it is surprising that this role has not been clarified in a clinical study context. A comprehensive search of the literature revealed only one clinical study (co-written by this author) comparing effects of thiamine alone versus thiamine and magnesium sulphate on Red Cell Transketolase (TKA) in alcoholic patients**.** [12] In this study, a more rapid recovery of the thiamine dependent enzyme Red Cell TKA occurred, when 2 grams magnesium sulphate was delivered simultaneously with thiamine than in a similar patient group treated with thiamine alone, however this study was not fully controlled.

The Scottish Intercollegiate Guidelines Network (SIGN) also identify the dosage and duration of Thiamine administration as an area of research to be encouraged.[13] The role of Mg^{2+} as an essential cofactor has a definite relevance to this question as Mg^{2+} may be influential in determining efficacy.

In this study we would like to extend out previous work by randomising alcoholic patients to treatment with either thiamine alone, magnesium sulphate alone (with delayed thiamine), or

concurrent administration of thiamine plus magnesium sulphate, to determine whether treatment with magnesium sulphate has any effect on its own on red blood cell transketolase activity, or only acts to increase the effect of thiamine.

1.3 Study hypothesis

Hypothesis: That magnesium administration enhances the biochemical response to thiamine.

2. STUDY OBJECTIVES

This is a single-centre, randomised, parallel group study to determine the effects of

- IV thiamine
- IV magnesium sulphate
- IV thiamine plus IV magnesium sulphate

on red blood cell TKA in a cohort of alcoholic patients admitted through A&E.

- **Primary Objective**

  To determine whether Magnesium administration enhances the biochemical response to thiamine as measured by the activity of the enzyme transketolase in red blood cells

- **Secondary Objectives**
  - To determine effect of the administration of thiamine alone, magnesium sulphate alone, or both together on plasma lactate concentrations, vitamins A, B1, B2, B6, B9 B12, C, D, E and K and trace elements (copper, manganese, copper and zinc)

3. STUDY DESIGN

This is a 3- arm randomised, open label, controlled study in a cohort of alcoholic patients admitted through A&E. Patients will be randomised to concurrent infusion of one of the following:

- **Arm 1:** IV thiamine
- **Arm 2:** IV magnesium sulphate followed by delayed IV thiamine
- **Arm 3:** IV thiamine and IV magnesium sulphate

Thiamine will be administered as IV Pabrinex, a compound preparation which also contains B vitamins and vitamin C. Administration of IV Pabrinex is standard care in this patient group and magnesium sulphate is routinely co-administered at Glasgow Royal Infirmary.

3.1 Study Population

A total of 120 patients will be recruited to this study, with 40 being randomised to each arm i.e.

- **Arm 1:** IV thiamine (Pabrinex)
- **Arm 2:** IV magnesium sulphate followed by delayed thiamine (Pabrinex)
- **Arm 3:** IV thiamine (Pabrinex) and IV magnesium sulphate

Patients will be identified by ED staff on presentation to the ED.

3.2 Inclusion criteria

- Written informed consent
- Male or non-pregnant or breastfeeding females ≥18 years of age For women of child-bearing potential a negative pregnancy test will be required prior to treatment.
  (Women of non-childbearing potential are defined as those defined as women who are post-menopausal or permanently sterilised (e.g. hysterectomy, tubal occlusion, bilateral salpingectomy).
- Chronic alcohol dependence as confirmed by
  - FAST questionnaire
  - GMAWS scale

3.3 Exclusion criteria

- Unable to give consent
- Less than 18 years of age
- Chronic renal or hepatic failure/hepatic encephalopathy (investigator assessment as documented in past medical history i.e. Clinical Portal.)
- Known hypersensitivity or previous allergy to any of the active substances in either trial medication, or to excipients
- Severe concurrent medical condition that would prevent participation in study procedures (e.g. myasthenia gravis, clinically significant cardiac disease, or cardiac failure with severe pulmonary oedema)

3.4 Withdrawal of subjects

Participants have the right to withdraw from the trial at any point for any reason. Data collected up to the point of withdrawal will be retained. The investigator can also withdraw patients from the study intervention in the event of inter-current illness, protocol violations or any other relevant reasons.

3.5 Assessment and management of risk

As above, there are three arms to this study. Our previous study examined the effect of thiamine and magnesium, as compared to thiamine alone, on TKA activity. This demonstrated a significant increase in TKA activity in the magnesium and thiamine group as compared to the thiamine group. It is therefore necessary to include the magnesium sulphate arm to this study to confirm this effect was not directly attributable to Magnesium separately, and to elucidate the degree of synergism that may exist between magnesium and thiamine.

Alcoholism is a disease of malnutrition. Dietary deficiencies develop over weeks, months and years. We appreciate that the two hour delay to Pabrinex administration, represents a delay to standard treatment in the Magnesium group (with delayed Pabrinex). However there is no evidence in the literature to indicate that a real time delay of two hours may disadvantage a patient, or that a single treatment of Pabrinex can reverse the chronic changes associated with Vitamin B1 (Thiamine) deficiency. It is our view therefore that a two hour delay will not disadvantage the patients randomised to this group. Indeed a 2 hour delay is not uncommon in the Emergency Department (ED) for any treatment due to the acuity and volume of patients attending a busy inner city ED. All patients attending the ED should be treated and discharged within the 4 hour window, as dictated by the national access target for emergency care.

Patients will be identified at triage in order to ensure adequate time to recruit, consent and obtain repeat samples at the 2 hour time interval post administration of treatment whilst still meeting national targets. Eligible patients may therefore be seen earlier in their patient journey which may offset potential delays due to study involvement. The net effect will be that patients randomised to the Magnesium group, will therefore receive their Pabrinex at approximately the same point in their patient journey, as if the study were not ongoing.

Magnesium sulphate and pabrinex are routinely administered to this patient group in the ED at GRI.

4 TRIAL PROCEDURES

4.1 Patient identification and consent

Patients will be identified by ED staff on presentation and will be determined to be alcohol dependent (Fast Alcohol Screening Test questionnaire) or in alcohol withdrawal as determined by the GMAWS scale (appendix) as per standard practice. Patients will then be

approached about the study by a trained and appropriately delegated member of the ED team who will provide a Patient Information Sheet and go through the purpose of the study and what it would require of them, and have any questions they may have addressed. Patients will then be given up to 30 minutes to decide whether they wish to take part. If they agree to participate patients will then be asked to sign a study consent form by a member of ED/research team. Eligibility to participate in the study will be confirmed by appropriately trained and delegated medical staff.

4.2 Randomisation

Randomisation will be performed in advance by the study statistician and opaque envelopes detailing the subject number and treatment allocation prepared. Patients will be sequentially assigned a subject number once eligibility is confirmed and the corresponding treatment assignment envelope opened. The opened enveloped will be retained and attached to the patient's case report form (CRF)

4.3 Trial assessments

Patients who have consented to participate in the study will have all study procedures carried out in a single visit. Where the procedure differs for the respective groups this will be indicated in the schedule below

Part 1: Baseline Assessments

- Medical history
- Pregnancy test for female participants of child-bearing potential.
- Randomisation
- Blood samples for biochemistry
    - **Standard care:** FBC, U&E, LFT, Gamma GT, CRP, serum Magnesium, glucose and lactate, random cortisol and nutritional markers
    - **Study specific:** erthyrocyte TKA, thiamine and magnesium trace elements copper, manganese, and zinc and vitamin A, B1, B2, B6, B9, B12 C, D, E and K
- Blood sample eGFR and blood glucose
- Weight
- Physical examination

Part 2: Administration of study medicines

Patients will be randomised to one of the following regimes and infusions administered:

- **Arm 1:** IV thiamine (Pabrinex)

- **Arm 2:** IV magnesium sulphate and delayed Pabrinex
- **Arm 3:** IV thiamine (Pabrinex) and IV magnesium sulphate

Part 3: Post-intervention Assessments

Patients in all groups will then have repeat blood samples 2 hours (+/- 30mins) for biochemistry

- serum magnesium, glucose, cortisol and lactate
- erthyrocyte TKA, thiamine and magnesium,
- trace elements copper, manganese, copper and zinc
- vitamins A, B1, B2, B6, B9, B12, C, D, E and K

Part 4: Administration of delayed Pabrinex (Arm 2 only)

For patients randomised to Arm 2, (IV magnesium sulphate and delayed thiamine), Pabrinex will be administered after the second blood samples have been taken, approximately 2 hours (+/- 30mins) after completion of magnesium sulphate infusion.

Case report forms will be updated as appropriate.

4.4 Study Outcome Measures

4.4.1 Primary Outcome Measure

- The relative change in TKA pre- and 2 hours (+/- 30mins) post-administration of
    - IV thiamine
    - IV magnesium sulphate
    - IV thiamine + IV magnesium sulphate

4.4.2 Secondary Outcome Measure

- The relative change in lactate pre- and 2 hours (+/_ 30mins) post administration of
    - IV thiamine
    - IV magnesium sulphate
    - IV thiamine + IV magnesium sulphate
- Review of levels of routine biochemical, trace elements (copper, manganese, selenium, zinc) and vitamin (A, B1, B2, B6, C, D, E and K) markers pre- and 2 hours (+/- 30 mins) post administration of
    - IV thiamine alone
    - IV magnesium sulphate
    - IV thiamine + IV magnesium sulphate

5 LABORATORY TESTS

Analysis of U&E, LFT, gamma GT, CRP, serum magnesium, glucose and lactate will be carried out be the Core Biochemistry section in the Biochemistry department of Glasgow Royal Infirmary. The FBC will be carried out by the Haematology department of Glasgow Royal Infirmary. Samples will be transported to the laboratory using standard means and analysed routinely.

A full micronutrient screen will be carried out by the Scottish Trace Element and Micronutrient Diagnostic and Research Laboratory located within the Biochemistry department at Glasgow Royal Infirmary. A standard micronutrient screen includes vitamin A, E, C and K and copper, zinc and selenium in plasma, vitamin B1 and Mn in whole blood and vitamins B2 and B6 and selenium in red cells. Additional tests will be carried out to assess micronutrient status that are not part of a standard micronutrient screen. Non-standard tests include magnesium, zinc and selenium in red cells and red cell transketolase activity. Non gel, lithium heparin tubes will be required. Samples will be taken and clearly labelled "AToM Study". Samples will then be transported to the laboratory within four hours of collection using standard means. Laboratory reception staff will prepare the whole blood, plasma and packed red cell fractions for the standard micronutrient tests within 30 mins of sample arriving in specimen reception. The red cell samples for magnesium, zinc, selenium and transketolase activity will be prepared and stored at -70 °C until analysis. Standard micronutrient tests will be analysed within laboratory turnaround times (6-10 days) and results will be entered into telepath. Non-standard tests will be stored until enough are accumulated to constitute a batch at which time they will be analysed. Results will be stored by the laboratory.

Results of both standard and additional assays will be copied to the Care Report Form (CRF).

6. DRUG INFORMATION

Patients who are eligible for the study will be randomised to receive one of the following arms:

- **Arm 1:** IV thiamine (Pabrinex)
- **Arm 2:** IV magnesium sulphate followed by delayed thiamine (Pabrinex) administered after completion of post-intervention assessments.
- **Arm 3:** IV thiamine (Pabrinex) and IV magnesium sulphate

In Arm 3 IV Pabrinex and IV magnesium sulphate will be administered concurrently. There is limited data available on Y-site compatibility for Pabrinex and magnesium sulphate infusions

however, it has been standard practice at GRI to administer in this way for a number of years.
All study drug administration will be completed within the ED where full resuscitation facilities are available.

6.1 Blinding arrangements

This is an open label study. No participant blinding will be necessary as the outcome measures are biochemical..

6.2 Prescribing, preparation and administration arrangements

All study treatments will be prescribed on a hospital Kardex and administration documented in accordance with standard practice in NHS Greater Glasgow. Only those who are trained on the study protocol and delegated prescribing responsibilities by the PI may prescribe study medication.

Pabrinex and magnesium sulphate are routinely prepared in ED with the latter currently used at physician discretion for treatment in alcohol dependent patients and also in treatment of asthma, pre-eclampsia, heart arrhythmias. Nursing staff experienced in preparation of magnesium sulphate and Pabrinex may prepare either infusions. There is no requirement that they be delegated this task on the study delegation log as this is within the remit of routine practice within the GRI ED department.

6.3 Thiamine (Pabrinex)

6.3.1 Thiamine (Pabrinex) treatment schedule

Participants will be treated once only with Pabrinex Intravenous High Potency Solution for injection as per standard care in this patient group as detailed above. Any further treatment with Pabrinex will be in accordance with standard care and will fall outwith this study.

6.3.2 Rationale for chosen dose

Administration of Pabrinex on admission to ED is standard care for this patient group.

6.3.3 Administration

Pabrinex will be administered as an intravenous infusion. Two pairs (1 pair = ampoule no 1 + ampoule no 2)of 5ml ampoules will be added to 100ml of sodium chloride 0.9% and administered IV over 30 minutes. The prepared infusion should be inspected prior to administration to ensure absence of particulates. No dose modifications are permitted. The infusion rate may be adjusted as per standard practice.

6.4 Magnesium sulphate

6.4.1 Magnesium sulphate treatment schedule

Participants will be treated once only with magnesium sulphate.

6.4.2 Rationale for chosen dose

Magnesium sulphate is currently used at physician discretion for treatment in alcohol dependent patients in GRI as part of standard treatment approach

6.4.3 Administration

Magnesium sulphate will be administered an intravenous infusion. Two grams of magnesium sulphate will be added to 100ml of sodium chloride 0.9% and administered IV over 30 minutes. The infusion should be inspected prior to administration to ensure absence of particulates. No dose modifications are permitted. The infusion rate may be adjusted as per standard practice.

6.5 Study supplies

6.5.1 Supply of study treatment

Magnesium sulphate and Pabrinex are already routinely available within the ED department. Supplies for the study will be sourced from usual ED hospital stock.

6.5.2 Labelling of study treatment

Prepared infusions should be labelled in accordance with standard practice.

6.5.3 Storage of study treatments

All supplies will be stored in accordance with the current Summary of Product Characteristics (SmPC).

6.5.4 Drug accountability

For traceability purposes, batch details for Pabrinex, thiamine and infusion fluid will be recorded on the CRF. No other accountability will be required.

7. PHARMACOVIGILANCE-

7.1 Definitions of adverse events

Adverse Event (AE) – Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

7.2 Serious Adverse Event (SAE)

Any adverse event or adverse reaction that:

a. results in death
b. is life threatening
c. requires hospitalisation or prolongation of existing hospitalisation
d. results in persistent or significant disability or incapacity
e. consists of a congenital anomaly or birth defect
f. is otherwise considered medically significant by the investigator
g. Important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

7.3 Recording and reporting of Adverse Events

AEs must be recorded, assessed, reported, analysed and managed in accordance with the Research Governance Framework for Health and Community Care and the study protocol. All AEs must be assessed for seriousness.

7.4 Serious adverse event and serious adverse reactions recording and reporting

Where an SAE requires recording, full details including the nature of the event, start and stop dates severity, relationship to research product and/or procedures. Outcome will be recorded in the patient's CRF (and medical notes where available). These events will be monitored and followed up until satisfactory resolution and stabilisation. SAEs must be assessed to determine if related to the research procedures (includes administration of study medicines) and expectedness.

- **Related:** that is, it resulted from administration of study medicines or any of the research procedures,
- **Expectedness for SAR:** that is, the expectedness of an adverse reaction to administered research products is assessed against the SmPC for Pabrinex and Magnesium sulphate.

- **Expectedness for SAEs:** is against the research procedure events listed in the study protocol as an expected occurrence.

All SAEs and SARs must be reported to the Pharmacovigilance Office immediately (within 24 hours) using the generic non-CTIMP SAE form which is available from http://www.glasgowctu.org/data/SAE_non-CTIMP.pdf . The SAE form should be completed and signed by appropriately delegated staff. The form should be faxed or e-mailed to the PV Office (pharmacovig@glasgowctu.org) and a copy placed in the Study Site File. If necessary a verbal report can be given by contacting the PV Office on 0141 330 4744. This must be followed up as soon as possible with a signed written (or electronic) report.

If all of the required information is not available at the time of initial reporting, the CI (or designee) must ensure that any missing information is forwarded to the PV Office as soon as this becomes available. The report should indicate that this information is follow-up information for a previously reported event.

7.5 Reporting of SARs and SAEs to the Ethics Committee

Reports of SARS and SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the 'report of serious adverse event form' for non-CTIMPs published on the Health Research Authority web site. http://www.hra.nhs.uk/documents/2015/02/safety-report-form-non-ctimp.docx The form should be completed in typescript and signed by the Chief Investigator.

7.6 Annual progress reports

The Chief Investigator must also provide an annual progress report to the REC. A report on the safety of participants will be included as part of this report.

7.7 Reporting to the MHRA

Whilst there is no statutory requirement to report to the MHRA adverse reactions to Pabrinex and thiamine may be reported to the MHRA Yellow Card Scheme (www.mhra.gov.uk/yellowcard).

8. STATISTICS AND DATA ANALYSIS-

8.1 Power and Sample Size

Choosing the higher standard deviation to be more conservative, a three group study was designed to detect a minimum biochemically significant difference of 0.16 in the change from

baseline between the groups, with 80% power and a 5% significance level. This requires 37 participants to be randomised to each arm of the study. We therefore propose a total sample of 120 to account for any drop-outs or missing data.

8.2 Statistical analysis plan

The following data was available from a pilot study for a two group design:

Descriptive Statistics: Combined, Thiamine

Variable	N	Mean	SE Mean	StDev	Minimum	Maximum
Combined	18	0.3211	0.0513	0.2176	0.0200	0.7500
Thiamine	12	0.1433	0.0350	0.1214	0.0100	0.4500

Power and Sample Size

Choosing the higher st dev to be more conservative, a three group study was designed to detect a minimum biochemically significant difference of 0.16 in the change from baseline between the groups, with 80% power and a 5% significance level. This requires 37 participants to be randomised to each arm of the study. We therefore propose a total sample of 120 to account for any drop-outs or missing data.

9.0 STUDY CLOSURE / DEFINITION OF END OF TRIAL

The study will end when one or more of the following situations applies:

- Last patient last study visit;

OR

i. There is insufficient funding to support further recruitment, and no reasonable prospect of additional support being obtained;
ii. New information makes it inappropriate to continue to randomise patients to one or other arm of the trial;
iii. Recruitment is so poor that completion of the trial cannot reasonably be anticipated.

10 DATA HANDLING

A paper case report form (CRF) will be used to collect study data. The paper CRF will be developed and managed by the study team. It is the investigator's responsibility to ensure completion and to review and approve all data captured in the CRF.

10.1 Record Retention

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records), all original signed informed consent forms, serious adverse event forms, source documents, and detailed records of treatment disposition in accordance with ICH GCP, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. Data will be retained for a minimum of 5 years.

11.0 TRIAL MANAGEMENT

11.1 Routine management of trial: Trial Management Group

The trial will be coordinated by the chief investigator. A Trial Management Group consisting of chief investigator R&D coordinator, R&D pharmacy staff and others as appropriate will be convened on an ad hoc basis. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

12. STUDY AUDITING

The Sponsor, NHS GG&C, carries out risk assessment on all studies to determine requirement ofr monitoring/auditing, and in addition carried out audit of studies on a random basis (approximately 10% of sponsored studies per annum).

13. PROTOCOL AMENDMENTS

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the CI following discussion with the Sponsor and any required amendment forms will be submitted to the regulatory authority, ethics committee and sponsor. The CI will liaise with study sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI

and Sponsor representative. Before the amended protocol can be implemented favourable opinion/approval must be sought from the original reviewing REC and Research and Development (R&D) office(s).

14. ETHICAL CONSIDERATIONS

14.1 Ethical conduct of the study

General:

The study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996] and Edinburgh[2000]).

Favourable ethical opinion will be sought from an appropriate REC before patients are entered into this clinical trial. Patients will only be allowed to enter the study once either they have provided written informed consent. The CI will be responsible for updating the Ethics committee of any new information related to the study.

15. INSURANCE AND INDEMNITY

This study is sponsored by NHS Greater Glasgow & Clyde. The sponsor will be liable for negligent harm caused by the design of the trial. NHS indemnity is provided under the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS).

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for clinical negligence and other negligent harm to patients under its duty of care.

16. FUNDING

No external funding has been sought. The study is supported by the A&E and Biochemistry departments of NHS Greater Glasgow and Clyde.

17. ANNUAL REPORTS

Annual reports will be submitted to the ethics committee and sponsor with the first submitted one year after the date that all trial related approvals are in place.

18. DISSEMINATION OF FINDINGS

It is hoped to publish study results in a peer reviewed journal and present at scientific meetings.

19. REFERENCES

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APPENDIX A:

Patient details : CHI / age

P/C: alcohol withdrawal, seizure, fall, recurrent falls , head injury, sepsis

PM/SH:

Have you been prescribed thiamine?

Do you regularly take thiamine or multi-vitamin tablets?

Medications: Antacid stomach medication PPi/H2 antagonist , Loop diuretics, Digoxin

Approximate Time of last alcoholic drink:

Predisposing poor nutritional status: Eating disorder, Opiate dependence

GMAWS score: