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Embedded Point of Care Randomisation for Evaluating Comparative Effectiveness Questions: PROSPECTOR-Critical Care Feasibility Study Protocol

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Key Words:

Electronic Health Record Trials; Point of Care Randomisation; Comparative Effectiveness Research; Learning Health Systems

Abstract

Introduction

Integrating clinical trial infrastructure within electronic health record systems enables trials to be conducted at reduced financial cost. This is crucial for Comparative Effectiveness Research investigating routine treatment strategies with little economic incentive for change. To date, embedded trials have focused on automating data collection, participant identification, and eligibility screening, but randomisation and consent continue to be manual. As both these key processes require staff time, scaling studies appropriately remains expensive.

This feasibility study will investigate a system for facilitating flexible randomisation at the point of clinical decision making. It will evaluate two designs of electronic randomisation prompt and explore two models of consent for Comparative Effectiveness Research.

The study uses an exemplar research question comparing the effectiveness of liberal or restrictive approaches to magnesium supplementation for the prophylaxis of atrial fibrillation in the critical care setting, a practice with demonstrable wide variation, without clear justification.

Methods and analysis

We will conduct a single centre mixed-methods feasibility study. Patients undergoing elective surgery requiring postoperative admission to critical care will be recruited. Following postoperative admission to critical care, participants will be randomised to one of two electronic point-of-care randomisation prompt designs, and then to liberal or restrictive magnesium supplementation strategies. Randomisation prompts will be displayed to the bedside critical care nurse at defined intervals.

The primary outcome will be the proportion of prompts resulting in compliance with the stated randomised allocation.

Secondary outcomes include acceptability of electronic point-of-care randomisation to clinicians, preferences on prompt design, and acceptability of pre-emptive and opt-out consent models.

Ethics and dissemination

This study was approved by the Riverside Research Ethics Committee (Ref: 21/LO/0785) and will be published on completion in a peer-reviewed journal.

Registration

This study is sponsored by the University College London Joint Research Office (Ref: 142382) and registered on ClinicalTrials.gov (Ref: NCT05149820).

Strengths and Limitations of this Study

- This study will advance understanding of how electronic health record systems may be used to deliver rigorous learning from routine clinical decision making by integrating a flexible approach to randomisation at the point of care.

- This study will investigate the design of electronic randomisation prompts, balancing the need to minimise alert burden and disruption of normal clinical care pathways.

- This study will evaluate patient attitudes towards alternative approaches to consent for comparative effectiveness research, contributing to the ongoing debate in the literature regarding the requirements for consent in areas where quality improvement and service evaluation overlap with clinical research.

- This study focuses on the use of these tools within the critical care environment but will represent a test case for deploying these tools across multiple domains in secondary care.

- This study will collect pilot data to allow planning of a large-scale trial of magnesium supplementation strategies in the future.

Introduction

Everyday clinicians collectively make hundreds of thousands of decisions regarding the application of treatments and interventions in the care of patients. Whilst the application of some of these treatments will be guided by robust evidence derived from Randomised Controlled Trials (RCTs), many of the treatments that might be considered part of "routine" clinical care continue to lack a strong evidence base [1]. Braithwaite et al describe this as the "60-30-10" challenge - that approximately 60% of administered treatments conform to evidence, 30% may be wasted or ineffective, and 10% result in patient harm [2].

When evidence for an intervention is not present, clinicians vary in their decision making according to their experience and preferences [3]. This variation is manifestly observable and can be seen across multiple domains from choice of surgical procedure [4,5], strategies for management of heart failure or diabetic ketoacidosis [6,7], or preferences surrounding antibiotic and intravenous fluid administration [8,9].

One example of variation in practice for a routinely administered treatment is the use of supplemental magnesium for the prophylaxis of atrial fibrillation in critical care patients. Whilst this practice is commonplace, the only reliable evidence as to its effectiveness comes from the post-cardiac surgery population [10]. Over time, this has been extrapolated to *all* critical care patients without additional evidence of benefit. As such, clinicians vary in their threshold for routine supplementation of magnesium. Given that the interaction between the timing of an individual patient's illness and an individual clinician's schedule is largely random, we reason that a patient's exposure to thresholds for magnesium supplementation is also random. Behaviour will be consistent at very high and very low measured magnesium levels (never supplement / always supplement), but within a 'normal' range the decision to supplement will have a random component [11].

Variation in practice does not necessarily imply substandard care - it may be that the clinician's experience offers benefits in optimising treatment delivery, or it may be that there is no meaningful difference between treatment choices. Under ideal conditions, clinicians would be able to learn from this variation, and improve the quality and coverage of evidence for future patients. Ineffective yet costly treatments could be minimised, and strategies demonstrating effectiveness targeted to ever smaller subgroups of patients.

Unfortunately, generating such evidence and learning from clinical decision making has proven difficult using existing research methodologies. RCTs are well suited to demonstrating treatment

efficacy in homogenised cohorts under tightly defined treatment protocols, but have proven costly and difficult to conduct in more pragmatic settings [12]. Whilst the classical RCT remains ideal for the evaluation of new or repurposed therapies, for treatments already in widespread use, with potentially small effect sizes, the expense of conducting comparative effectiveness trials becomes untenable. In most cases, researchers have then relied on observational techniques, which lack the validity derived from experimental randomisation [13]. As such, to properly evaluate the comparative effectiveness of multiple treatment strategies, an element of randomisation is required, together with a mechanism to deploy this efficiently [14].

Electronic Health Record Systems (EHRS) have presented a solution. As they become increasingly widespread and comprehensive, interest in integrating clinical trial infrastructure has blossomed [15]. Whilst embedding clinical trial infrastructure, notably data collection, has improved trial efficiency, the requirement for point-of-care consent and randomisation remains. In the main, this continues to be delivered by a research nurse, in partnership with the treating clinician, a process which remains time intensive, and financially costly [16]. To date, we have yet to find a methodology which streamlines this crucial step without affecting safety or compromising the ethical principles underpinning medical research. As such, despite advances in RCT design and implementation, the routine evaluation of frequently occurring clinical decisions remains beyond reach.

Two barriers to implementing routine comparative effectiveness research standout – 1) how to fully integrate randomisation into the EHRS, ensuring that patient safety and the scientific integrity of the study is maintained; and, 2) what is the correct way for patients to consent to the randomised delivery of routine treatments? Key to addressing these issues is principle of clinical equipoise – the idea that without evidence, every clinical decision comes with a degree of uncertainty. When the benefits and risks of the treatment are balanced (or unknown), then it becomes justifiable to randomise in order to learn what decision is best [17,18].

Flexible Electronic Point-Of-Care Randomisation

To learn effectively from clinical decisions, we need a rapid and responsive randomisation mechanism. To achieve this, we propose a two-stage innovation: 1) to embed the randomisation process into the EHRS and link randomisation to the moment of clinical decision making, and 2) to make that randomisation optional for the clinician. The first step means the prompt to randomise is presented to the clinician *at the point of potential equipoise*. Step two means that the clinician-patient dyad only access the randomisation process if they share the position of equipoise with the trial.

Historically, clinical trials rely on the presence of "group equipoise" – members of the clinical team are presented with a trial question and decide *en masse* whether to participate, principally based on whether there is shared equipoise for the trial question. This ensures the trial is feasible, as most clinicians will comply with the randomised allocation when confronted with the treatment question (particularly if the trial is not blinded). However, for the evaluation of routinely administered treatments, clinical equipoise is a particularly fluid concept, often being highly specific to the clinician, patient and treatment question. Classical trial designs do not permit clinicians to express equipoise in a flexible manner, where clinicians disagree this often results in a protocol violation.

To intercede in clinical decisions within the EHRS without becoming overly burdensome requires understanding of how clinicians interact with the EHRS, and how clinical data is used to make decisions. Once this is understood, existing tools within most EHRS may be adapted to deliver a randomisation prompt. In the case of magnesium supplementation in critical care, this is most often driven by the bedside critical care nurse, who interacts with the EHRS when viewing the patient's daily serum magnesium level (one of the primary drivers behind the decision to supplement or not), or in accessing the magnesium prescription. Any attempt to intercede in this process must therefore cover both these avenues.

Many comprehensive EHRS have built in resources to deliver information to clinicians or alert them to particular conditions in a time sensitive manner. These clinical decision support systems come in many forms but use the same format of logical rules to allow them to display to the clinician under pre-defined circumstances. These logical rules may be used to emulate inclusion and exclusion criteria within a clinical trial. Once designated conditions are met, a modified prompt/alert/advisory can be displayed to the clinician, at the point of clinical decision making, to highlight both the *opportunity* to randomise and present the predetermined treatment group *allocation*.

In a standard RCT, clinicians retain overall responsibility and control over whether a participant receives the treatment or not, ensuring patient safety. To reproduce this within our proposed trial design, our electronic randomisation prompt will allow a flexible approach to following randomisation. This electronic Point-Of-Care Randomisation (ePOCR) prompt will invite the clinician to consider whether they have clinical equipoise for the given decision, in a sense asking, *"are the relative benefits of giving or not giving this treatment balanced or unknown in this particular instance?"*. In this way, the prompt simply externalises and makes explicit the normal decision-making process.

If the clinician agrees there is equipoise, the ePOCR prompt allows the clinician to view the randomised allocation, which can then be followed and contribute to the experimental arm of the study. However, where the clinician lacks equipoise, they remain free to follow their preference. In a classical RCT,

declining to follow the randomised allocation may represent a protocol violation and result in the participant being excluded from the final analysis. However, in our proposed design, the participant continues to contribute data as the effects of the clinician declining randomisation are observed.

Hence, when the clinician agrees with the randomised allocation, the participant contributes data to the RCT arm of the study. When the clinician declines randomisation, the participant contributes data to an observational study arm. This observational arm continuously evaluates external validity and can identify previously unrecognised subgroups where clinicians have strong preferences that may require modification of the trial. This flexible approach to delivering randomisation is depicted in **Figure 1**.

Pre-Emptive and Opt-Out Consent

There is ongoing debate as to the most appropriate consent mechanism for facilitating comparative treatment effectiveness research, in particular those treatment questions where a substantial degree of variation is already present in their application. In particular, work by Faden and colleagues highlights both the strong ethical arguments in favour of streamlining consent procedures in this area and the acceptability to different stakeholders of the same [19–22].

In this study we will investigate moving the point at which consent is obtained proximally, away from the final application of eligibility criteria and randomisation. A future model might see patients routinely consented for a range of potential CER trials (under a specific operational framework, such as that suggested by Fiore and Lavori [14]) on admission to hospital, before it is known whether or not they will be eligible. This single point of contact would decrease the burden of identifying and consenting patients and minimise disruption to clinical workflows. In the case of severe illness, there are often periods when patients lack the capacity to consent, and direct consent alternatives are already routine and justified [23].

Study Objectives

The primary objective of this study is to determine the effectiveness of two designs of ePOCR prompt (Nudge vs. Preference designs). The secondary objectives are to evaluate the acceptability of ePOCR to clinicians, ascertain clinician preference for prompt design, ascertain patient views on the acceptability of pre-emptive and opt out consent models for CER, and collect pilot data to inform a future main trial design.

Methods and Analysis

Study Design and Setting

This single centre, mixed methods feasibility study will follow an explanatory-sequential design. This aims to gather quantitative data on the effectiveness of ePOCR prompts and use accompanying before-and-after qualitative data to aid interpretation. This study will be conducted at critical care units within University College London Hospitals NHS Trust. The study will be pragmatic in nature, with minimal disruption to usual care pathways.

We will recruit patients aged 18 years or over, who are undergoing elective surgery of complexity sufficient to routinely warrant post-operative admission to a critical care unit. This cohort was selected opportunistically to facilitate obtaining informed consent *pre-emptively*, prior to surgery and critical care admission. Potentially eligible participants will be identified through a combination of algorithmic screening of the EHRS by surgical procedure code, and by manual identification from booked critical care admissions. Potentially eligible patients will be approached by a designated member of the research team, mediated by clinicians in Pre-Assessment Clinic.

Exclusion criteria will be applied at two stages throughout the study. Patients who are unable to provide written informed consent, or who are pregnant will not be recruited. Following postoperative admission to critical care, patients whose initial documented heart rhythm is atrial fibrillation will be excluded. Prior to the deployment of each randomisation prompt, participants' electronic health record data will be automatically screened against the following criteria: 1) no documented allergy or intolerance to any preparation of supplemental magnesium, 2) no active treatment for bronchospasm (defined as active treatment administration indicating bronchospasm and screening of active problem list), and 3) the most recent serum magnesium laboratory result, prior to prompt deployment lies between 0.5 and 1.5 mmol/L. This final criterion is to ensure that the prompt does not offer the opportunity to randomise for values outside the scope of reasonable clinical equipoise. For example, serum magnesium values < 0.5 mmol/L would normally always be supplemented and vice versa for values > 1.5 mmol/L.

If these criteria are satisfied, the EHRS will permit the randomisation prompt to deploy to the clinician. This process is repeated for each new serum magnesium laboratory result received for the individual patient, and the screening criteria are applied for each new result. This process is illustrated in **Figure 2**.

Qualitative assessments will be conducted in three stages. All critical care clinicians involved in the routine postoperative care of patients will be invited to undertake an initial interview. Two further interviews focus specifically on the bedside critical care nurses exposed to the ePOCR prompt.

Interventions

Electronic Point-Of-Care Randomisation Prompts

This study will compare 'Nudge' and 'Preference' ePOCR prompts against their ability to generate compliance with randomised allocations to liberal or restrictive magnesium supplementation strategies. Both prompts are deployed to the bedside critical care nurse following the same common pathway. Following admission to the critical care unit, participants will be randomised between Nudge or Preference prompt, and to a liberal (supplementation at serum magnesium < 1.0 mmol/L) or restrictive (supplementation at serum magnesium < 0.75 mmol/L) strategy, as shown in **Figure 3**. Randomisation will be undertaken using built in functionality within the EHRS, which conducts simple randomisation using an internal number rule [24]. For the purpose of this feasibility study, basic randomisation, without additional covariate balancing will be used.

Once the EHRS detects a new serum magnesium result it will screen the participant against the remaining exclusion criteria. If these criteria are satisfied the prompt will activate and display to the bedside nurse under either of two conditions: 1) accessing of the participants blood test results within the EHRS, or, 2) accessing the supplemental magnesium prescription within the EHRS. The prompt will deploy for each new serum magnesium laboratory result, for five post-operative days or the end of the patient's critical care admission, whichever is sooner.

Two ePOCR prompt designs are considered in this study. The Nudge design is characterised by its passive nature and requires minimal interaction from the clinician following deployment. The intention is to 'nudge' the clinician to consider if they have equipoise for the decision to administer supplemental magnesium, at the randomly allocated threshold serum magnesium value. **Figure 4** illustrates an example ePOCR prompt where the participant has been randomised to receive the Nudge design and allocated to the Liberal magnesium strategy arm.

In contrast, the Preference design facilitates the explicit recording of the clinician's preference for the magnesium supplementation decision, whilst simultaneously allowing the clinician to reveal the randomised allocation under conditions of clinical equipoise. The advantage of this design is the

explicit collection of preference data; however, this is tempered by requiring the clinician to engage with a multi-step process, including actively clicking on their preferred choice - a potentially more burdensome design, which may be more disruptive to normal care pathways. An example of the Preference design is shown in **Figure 5**. The clinician selects the most appropriate link, triggering a second prompt displaying further instructions. If the clinician selects the "no preference" option, the second prompt will display the randomised allocation in the same format as the Nudge design. Selecting a strong preference for or against supplementation will result in a second message informing the clinician to continue with treatment as per their decision.

For both ePOCR designs, participants will be further randomised between liberal and restrictive magnesium supplementation strategies, based on threshold serum magnesium values at which supplementation should be delivered. These values were determined from an observational study of supplementation practices at the study centre and fall within the boundaries of observed variation in practice [11]. In both supplementation arms, how magnesium is supplemented will remain at the discretion of the clinical team. At our institution it is normal practice for all patients admitted to critical care to be issued with an "as required" prescription for either intravenous or oral magnesium. The route, dose and frequency of the prescription remains unaltered within the study, as does frequency of monitoring serum magnesium levels.

Qualitative Assessments

Both clinician and patient interviews will follow a semi-structured design. Prior to ePOCR deployment, critical care clinicians will be invited to undertake an interview exploring general attitudes towards electronic health record research and their current interactions with existing electronic alerts and prompts. As part of this interview, each clinician will undertake a guided simulation introducing both prompt designs and encouraging them to give initial feedback. The use of guided simulation to introduce the prompts acknowledges the logistical difficulty in ensuring that each critical care nurse is exposed to each prompt design in the clinical environment at least once during the study period.

Bedside critical care nurses will then undertake a further interview following exposure to an ePOCR prompt to gather immediate feedback. A final follow up interview will invite nurses to give a preference on prompt design, having experienced their use in a clinical setting.

Patients participating in the study will be asked to undertake a semi-structured interview following discharge from critical care, for the purpose of exploring their attitudes towards pre-emptive and opt-

out consent models. Detailed schedules for clinician and patient interviews are included in **Supplementary Materials S1**.

Outcomes, Data Collection & Analysis

The primary outcome will be the proportions of ePOCR of each design which result in a successfully randomised action by the clinician, relative to the total number of deployed prompts. Estimates of compliance with the prompt will be generated for both magnesium strategies and both prompt designs. Compliance is defined as either: 1) the appropriate administration of magnesium, following prompt deployment in the EHRS, where the measured serum magnesium is less than the randomised threshold; or, 2) the appropriate withholding of supplemental magnesium following prompt deployment, where the serum magnesium is greater than the randomised threshold. The potential outcomes following prompt deployment and their classification into complier/defier groups are illustrated in **Figure 6**, using the Nudge prompt as an example. Identification of compliance in the Preference prompt will function in the same way, except only instances where the clinician has indicated "no preference" will be included. Where the clinician expresses a strong preference, the resulting action (administration of magnesium or not) will be observed and recorded within the study, to demonstrate the link between preference and action.

Data pertinent to the primary outcome (magnesium administration following ePOCR prompt) will be extracted from the EHRS. Except for the interview data, no additional data items will be recorded beyond those routinely collected through clinical care. We will collect pilot data pertinent to planning a future adequately powered trial, including baseline rates of atrial fibrillation in the study population, frequency of serum magnesium measurement, rates of supplementation and estimates of treatment group separation (difference in mean serum magnesium values between liberal and restrictive groups).

The program of semi-structured interviews will contribute qualitative data addressing both primary and secondary outcomes. Overall success of the ePOCR design will be a composite of the prompt compliance value (indicating success at generating completed randomisation events) and acceptability to clinicians. ePOCR compliance data will be used to inform estimates of sample size requirements for a future main trial, which will further demonstrate the feasibility of this study design.

We will analyse qualitative data using a thematic analysis approach as described by Braun and Clarke and illustrated in a recent analysis by McNulty et al [25].

The primary study objective addresses the effectiveness of ePOCR prompts. We will not seek to answer the question of relative superiority of either magnesium supplementation strategy within this feasibility study. As such, sample size has been chosen pragmatically based on a six-month study duration. Patient and clinician recruitment will be continuous over this period. Assuming two suitable operating lists per week, each comprising four potentially eligible participants, and estimating a 50% recruitment rate suggests a potential sample size of 88 patients. Allowing for difficulties with recruitment, dropouts and loss to follow up we aim to recruit a total of 50 patients, which should be sufficient to demonstrate feasibility of our study design. We aim to recruit the same number of critical care nurses to complete interviews but will aim to recruit additional clinicians to the initial interview to gain a more comprehensive overview of study acceptability.

Ethics and Dissemination

This study protocol was approved by the NHS Riverside Research Ethics Committee (Ref: 21/LO/0785) and sponsored by University College London (Ref: 142382). Main issues of study design and methods of informed consent were presented to two separate patient and public involvement groups for discussion, coordinated by the University College London Patient and Public Involvement team. Both groups provided feedback which improved the clarity and communication of the study principles, for which the authors are extremely grateful. We plan to enlist two patient representatives to provide ongoing support to this and future work.

Potentially eligible patients will be approached during their Anaesthetic Pre-Assessment Clinic appointment. After confirming ability to give informed consent, a member of the research team will discuss the study including written participant information sheet with the patient. The patient will be able to give written consent at time of discussion, or at an alternative point prior to surgery. The patient will be provided with contact details should they wish to discuss the study further or discontinue participation at any point.

By approaching patients during Pre-Assessment Clinic, we ensure a natural "cooling off" period prior to commencing the study. We additionally justify potentially obtaining consent at the initial visit in three ways. Firstly, the study premise and intervention carry minimal risk to the participant, second, the burden on the participant is low, namely one follow-up interview following surgery. Thirdly, we provide multiple routes to discontinue participation with multiple checks throughout the perioperative journey.

We ensure that participant data is protected by extracting only data pertinent to the study from the EHRS. All clinical data obtained during the study, including identifiable data will remain within University College London Hospitals computer infrastructure and firewall. Data extracted from the EHRS will only be available to designated members of the research team and presented as summary level data. Interview data will be audio recorded and uploaded to the University College London Data Safe Haven, a secure data environment conforming to NHS Digital's Information Governance Toolkit [26]. Following transcription, interview data will be de-identified and only anonymised quotes utilised in the study reports. We plan to disseminate research findings by publication in peer-reviewed journals and will also prepare reports for patients and clinicians involved in the study should they wish to receive them upon completion.

Author Contributions

All authors were involved in conceiving the research idea, developing the study design. SKH is the chief investigator for the study and MGW the principal investigator. MGW prepared the initial draft of this manuscript, and all authors were involved in contributing major edits. All authors have read and approved the final protocol and this manuscript.

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Competing Interests

The authors declare that they have no conflict of interest.

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Data Sharing Statement

Summaries of data analysis from the feasibility study will be available upon request.

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Figure 1 – Flexible Randomisation as an Expression of Clinical Equipoise

Figure 2 – Anticipated Participant Flow Through Study

Figure 3 – Two Stage Randomisation Process

Figure 4 – Example of the Nudge ePOCR Prompt Design

Figure 5 – Example of the Preference ePOCR Prompt Design

Figure 6 – Derivation of Compliance with Randomisation from Observed Clinician Actions

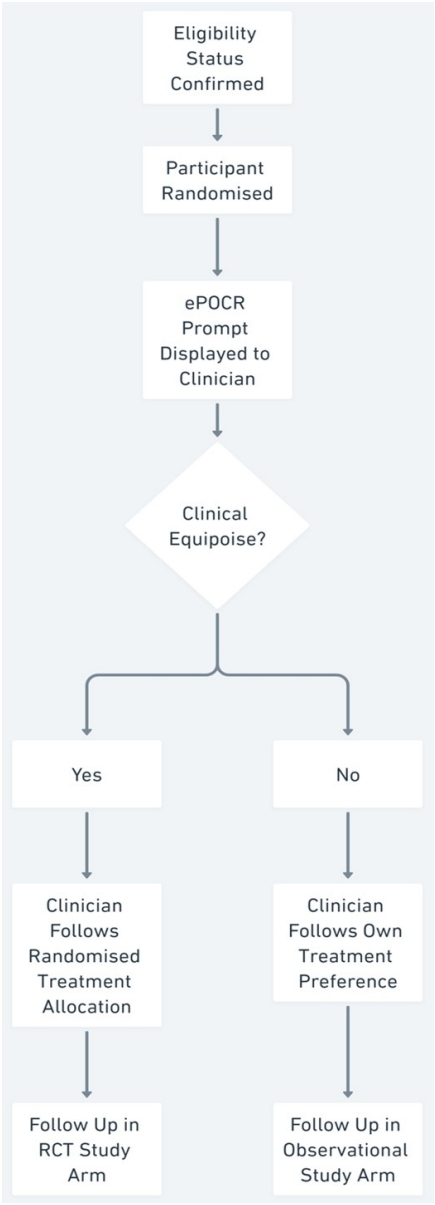

Figure 1 - Flexible Randomisation as an Expression of Clinical Equipoise

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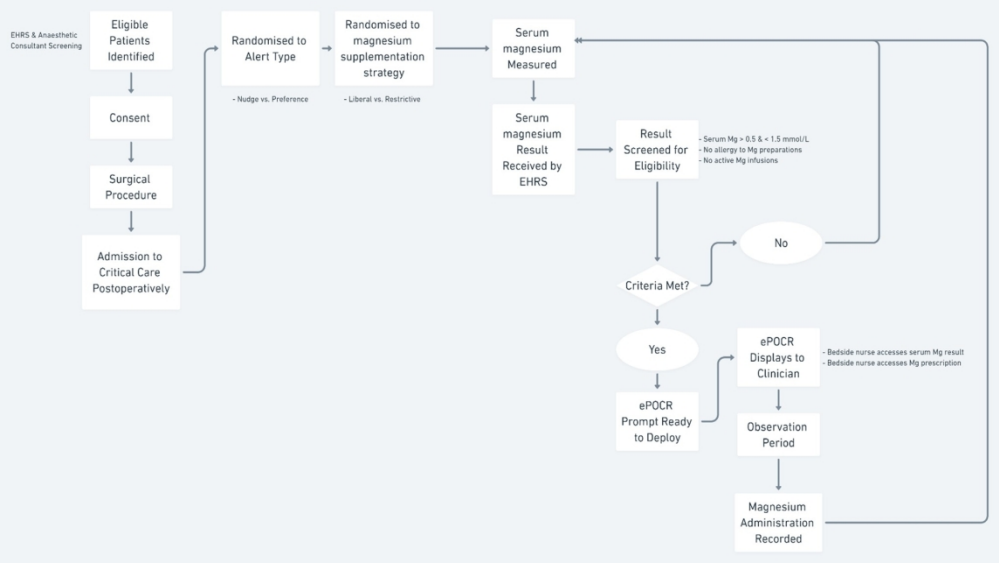

Figure 2 – Anticipated Participant Flow Through Study

235x132mm (220 x 220 DPI)

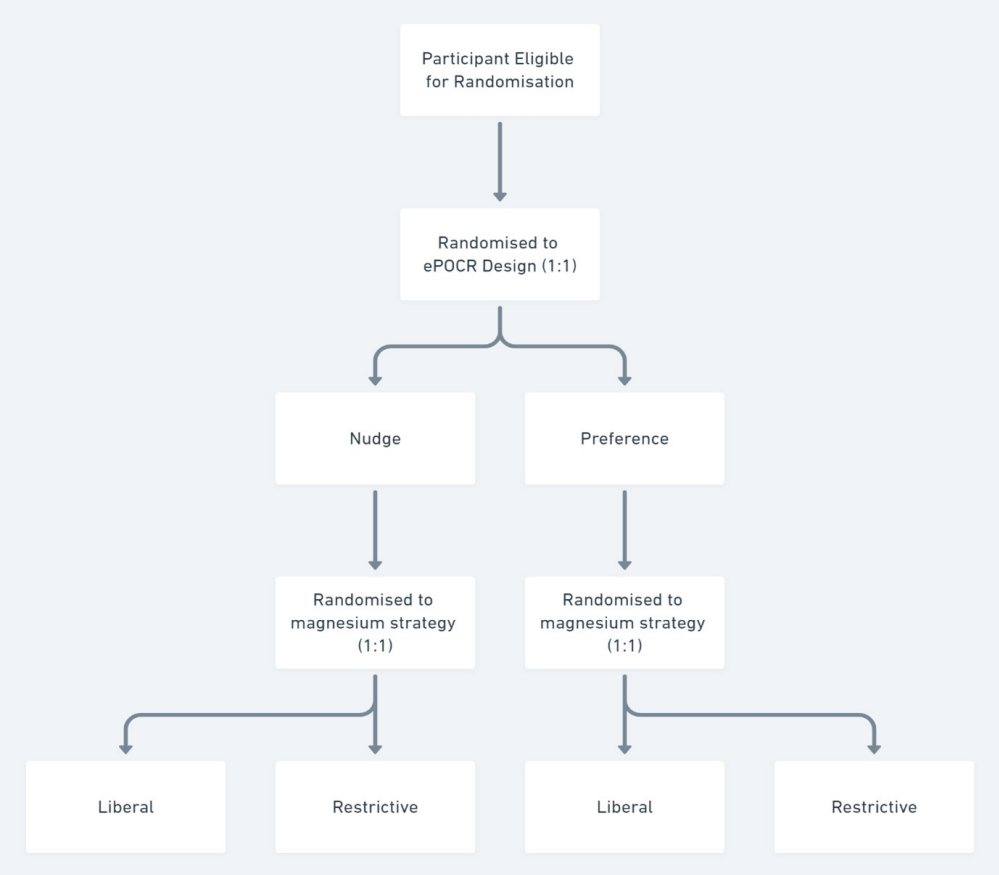

Figure 3 – Two Stage Randomisation Process

159x139mm (220 x 220 DPI)

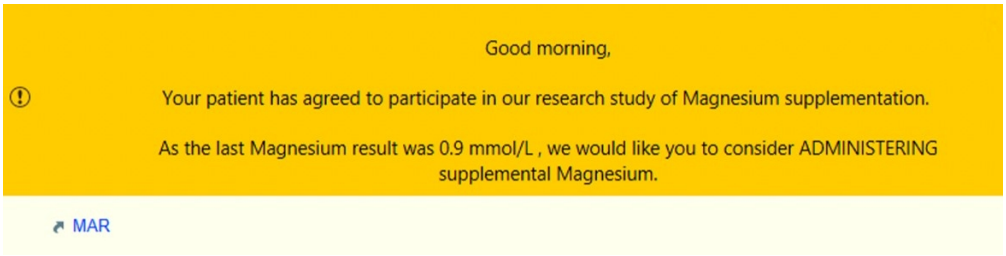

Figure 4 – Example of the Nudge ePOCR Prompt Design

176x44mm (168 x 168 DPI)

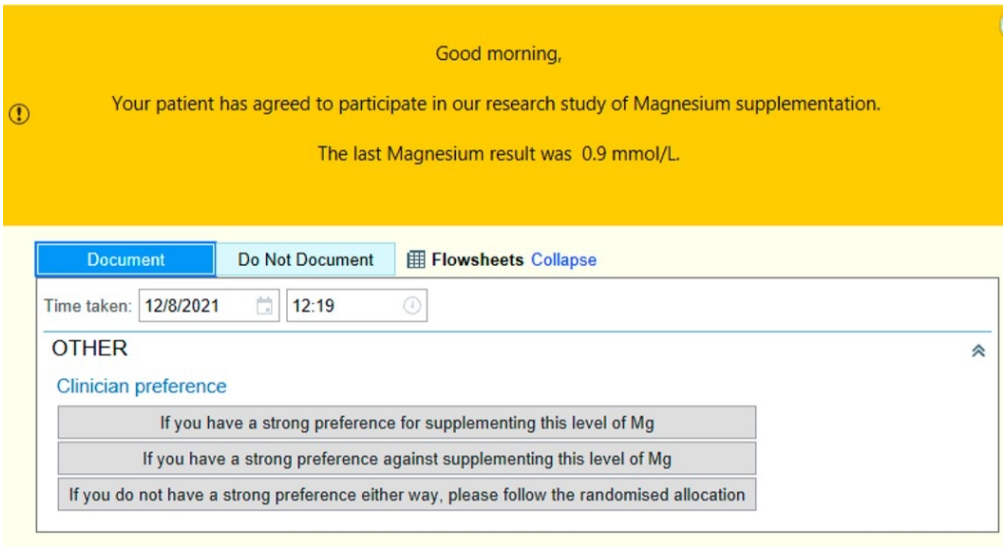

Figure 5 – Example of the Preference ePOCR Prompt Design

159x86mm (168 x 168 DPI)

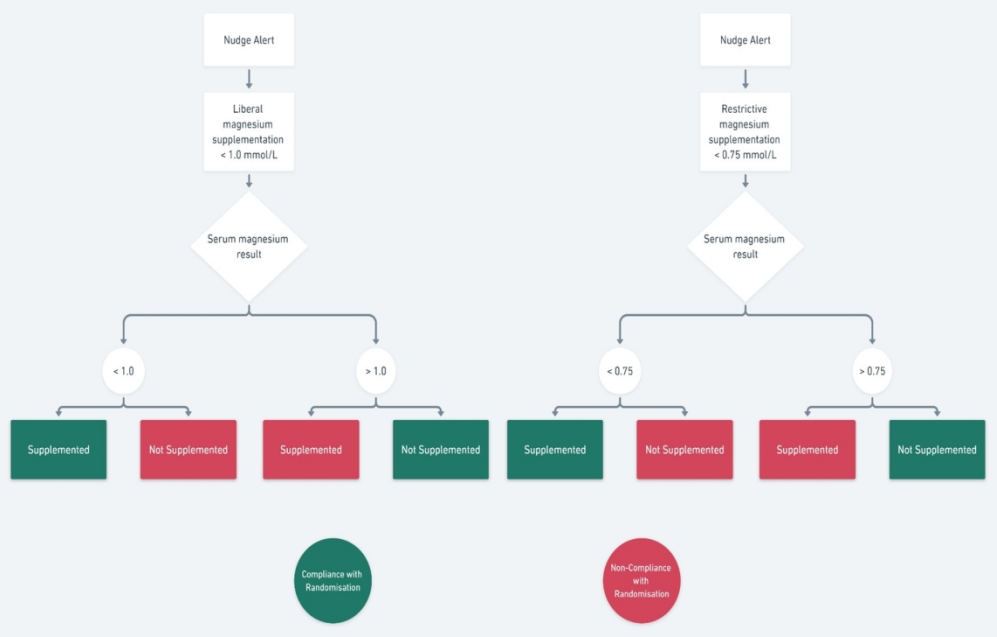

Figure 6 – Derivation of Compliance with Randomisation from Observed Clinician Actions

204x130mm (220 x 220 DPI)

Supplementary Materials

S1 Clinician & Patient Semi-Structured Interview Schedules

IRAS ID: 279737

Centre Number: 1

Study Number: 142382

Version Number: 1.0 (22.09.21)

PROSPECTOR-Critical Care - Clinician Interview Schedule

Design

Following recruitment, clinicians will be asked to participate in a three-stage interview process. The first interview will be open to all critical care clinicians. The remaining two interviews will focus on critical care nurses who interacted with the prompts during the intervention phase.

Pre-Intervention Interview

This will collect background information on the individual nurse, including seniority and critical care experience and interactions with clinical research and electronic health record systems, including Best Practice Alerts specifically. The nurse will be asked about their understanding of their current practices regarding supplementing Mg, drivers, and motivators for administration and specific questions to elicit their perceived zone of equipoise for administering Mg based on serum Mg levels.

After gathering baseline information, each clinician will undertake a guided simulation of each alert design as a demonstration. Following the simulation, participants will be asked for feedback on the alert principles and design aspects.

Post-Exposure Interview

Specifically directed at the critical care nurses interacting with the alert, this interview will take place following exposure to the alert, within the intervention phase of the study. It will focus on areas such

as usability, understanding and impact on the individual's clinical workflow. It will focus on highlighting reasons for compliance or defiance with the alert.

Follow-Up Interview

Following completion of the intervention phase, clinicians who were exposed to the alert will be invited to undertake a follow up interview. The purpose of this is to explore their overall attitudes towards the study and to garner qualitative comparison data on the two alert designs. It is likely that the majority of the participating nurse cohort will only be exposed to one of the two alert designs during the intervention period due to the scale of the study. To enable a comparison to be made, participants will be invited to review the simulation of the alert they did not interact with clinically during the interview. The use of simulated alerts for comparison will be recorded. The subgroup of nurses interacting with both alerts during the intervention phase will be presented in the results.

Pre-Intervention Interview

Aims

- Gather baseline information about clinicians

- Baseline qualitative data on attitudes towards Magnesium supplementation

- Guided simulation of both types of alert

- First-impression feedback on alert principles and design

Background

- Occurs following participant recruitment (nurses) or in isolation for other ICU clinicians.

    - Following review of Participant Information Sheet and Consent Form.

- Audio transcribed, simulation guided using Epic.

- Following interview completion, nurses will continue on to the intervention phase of the study, other ICU clinicians will complete study.

- Anticipated duration: 30 minutes

Semi-Structured Interview Schedule

> Before we start, can I check that you are happy to continue with the interview today?

> It should take approximately 30 minutes

> I'll be recording what we discuss so that it can be analysed with the rest of the study results after

> As per the Information Sheet, the audio recording will be uploaded to a secure electronic storage vault and won't leave that without being anonymised beforehand.

1. **What is your role in the ICU?**
    - **a.** If ICU nurse:
        - **i.** Number of years qualified.
        - **ii.** Number of years working in critical care.
        - **iii.** Banding.
        - **iv.** Duration worked in this ICU.
        - **v.** Number of shifts per week.
2. **Have you been involved in research studies for critical care patients before?**
    - **a.** Which ones?
    - **b.** What was your role?
    - **c.** Have you been involved in any research studies using Epic?
3. **Thinking about the routine treatments that we give to critical care patients daily, can you estimate the proportion of these that are underpinned by good quality evidence?**
    - **a.** How do you interact with evidence about the treatments you give?
        - **i.** Journals
        - **ii.** Clinical guidelines
        - **iii.** MDT/Teaching/Colleagues
4. **How do you interact with a patient's blood test results?**
    - **a.** Do you review them yourself (i.e. independently of the ward round for nurses).
    - **b.** Do you review them every shift?
    - **c.** How does reviewing blood tests integrate into your daily workflow?
        - **i.** Is there a particular time during each shift where you review them?
        - **ii.** Would you review them on a night shift?
        - **iii.** What kind of actions do you take from reviewing the blood test results?
5. **What are the main reasons you might administer supplemental Magnesium to a critical care patient?**
    - **a.** Clinical indications
    - **b.** What drives you to access the PRN Magnesium prescription?
6. **How often would you administer (or request) supplemental Magnesium?**
    - **a.** What proportion of your shifts?
    - **b.** What proportion of your patients?
7. **Do you ever consult anyone else about whether or not to give supplemental Magnesium?**
    - **a.** Who?
    - **b.** How often?
8. **Consider a patient's serum Magnesium lab result – do you have a threshold for giving Magnesium?**
    - **a.** Low (when you would always give)
    - **b.** High (when you would never give)
    - **c.** How would you decide what to do in between these values?
9. **Do you ever feel uncertain about what level of Magnesium to supplement at?**
    - **a.** Can you estimate the numbers around which you feel uncertain?

b. What makes you uncertain?
c. What do you do if you are not sure what to do?

10. What are your feelings about Epic as an Electronic Health Record System?

11. Do you interact with any pop-up alerts at the moment?

a. Which ones?
b. What do you think of them?
c. Do they ever prompt you to change your clinical practice?

> I'd like to show you two designs of electronic alert.

> These are designed to activate within Epic, under specific conditions - in this case, around the time that the ICU nurse is reviewing blood test results or considering administering supplemental Magnesium.

> I'll walk you through how the alerts activate, and how you might interact with them and then ask what you think about them.

> Walk through Nudge Alert.

> Walk through Preference Alert.

12. What are your initial thoughts about these two alerts?

13. Can you describe what the alert is asking you to do?

14. What do you think your response to the alerts might be?

a. For non-nurses, ask them to consider a similar research question relevant to their role to frame the question in more relevant terms.

15. Do you think these alerts will be disruptive to your clinical workflow?

Post-Exposure Interview

Aims

- Assess alert useability and understanding of the alert.
- Assess immediate feedback on clinical workflow impact.
- Assess reasons for compliance or defiance with alert.

Background

This interview is focused on critical care nurses who have interacted with one of the alert designs in a clinical setting. It is designed to be carried out within the same shift as the nurse receives the exposure. Intended duration: 15 minutes.

Semi-Structured Interview Schedule

1. **Did you receive any electronic alerts whilst looking after your patient today?**
    a. What were they?
    b. What were you doing when you received them?
2. **How did you feel when you received the Magnesium alert?**
3. **What was the Magnesium alert asking you to do?**
4. **Did you follow the suggestion of the alert?**
    a. Why?
    b. Did you feel that the alert was clear in what it was asking of you?
    c. Did you feel pressured to do something you weren't comfortable with?
5. **Thinking back to what you were doing when you received the alert: how did you feel about the timing of the alert activating?**
    a. Was it inconvenient? How would you fix it?
    b. Did you feel you had enough time to review it and consider what to do?
    c. Currently the alert deploys based on when you look at the blood test results or when you access the Magnesium prescription, can you think of better times or triggers for the alert to activate which might work better with your workflow?
6. **What did you do immediately following the alert?**
7. **How do you feel about how frequently the alert popped up?**
8. **What do you think of the design of the alert itself?**
    a. Easy to understand? // Unclear language? // Too much or too little information?
9. **Did you discuss the alert/decision to give Magnesium with any other members of the clinical team?**
10. **How do you think this alert impacted or changed the patient's care?**
11. **If the patient was able to, did you discuss the alert or decision to supplement Magnesium with the patient?**
12. **Would you routinely discuss Magnesium supplementation at handover?**

Follow Up Interview

Aims

- Explore overall attitudes towards the study.
- Compare and contrast alert designs and elicit preferences.

Background

This interview will be conducted following conclusion of the intervention phase and will be focused on participating critical care nurses who were exposed to an alert whilst delivering clinical care.

It is anticipated that nurses may not be exposed to both alert designs during the intervention period and as such this interview will include a second simulated walk through of the alert design not seen clinically to facilitate a comparison. Intended duration: 30 minutes.

Semi-Structured Interview Schedule

1. **During the course of looking after patients in this study, were you exposed to an electronic alert about Magnesium?**
    a. How many times did you receive the Magnesium alert in total?
2. **Were you exposed to two types of alert design at least once?**
    a. Show picture examples to aid recall.
    b. Can also compare against exposures from EHRS.

> At this point, if the nurse has not been exposed to one type of alert design, pause the interview and go back through the simulated walk through for the alternative alert type as a refresher.

3. **If you compare both designs of the alert, do you prefer one design over the other?**
    a. Why?
    b. What are the good and bad aspects of each design?
4. **Do you feel that one type of alert made you more likely to follow the randomised allocation over the other?**
5. **Do you think you were more likely to ignore one design over the other?**
6. **Overall, how have you found taking part in this study?**
7. **What do you think about the potential for using alerts like this to research routine treatments in ICU?**
8. **If we ran a larger scale version of this trial, with the aim of finding out if liberal or restrictive Magnesium supplementation was better at preventing Atrial Fibrillation:**
    a. Would you take part?
    b. Which alert would you pick to use?
    c. What do you think the result of the trial would be?

9. **Imagine we were using this design of experiment (with electronic alerts and randomisation) to investigate different ICU treatments at the same time. This means that you might get more than one alert for different treatments during a shift:**
    - **a.** What do you think about having more than one alert question running at once?
    - **b.** What do you think the maximum number of different alerts that would be tolerable is?
10. **Part of the process for picking research questions to investigate with this method is that we demonstrate a lack of evidence as to the best course of action, and existing variation in how clinicians administer the treatment. Consider each of these scenarios, would you be happy to use the alert randomisation method to investigate them?**
    - **a.** Randomising to different durations of postoperative antibiotic treatment to prevent surgical site infections.
    - **b.** Randomising to different thresholds of Haemoglobin at which to "top-up" with a blood transfusion.
    - **c.** Randomising to different thresholds of temperature at which to administer Paracetamol for a fever.
    - **d.** Randomising to different target mean arterial blood pressures for patients.
    - **e.** Randomising to different durations of non-invasive ventilation before intubation for patients with pneumonia.

IRAS ID: 279737

Centre Number: 1

Study Number: 142382

Version Number: 1.0 (22.09.21)

PROSPECTOR-Critical Care - Patient Interview Outline

Aims

Evaluate acceptability of *pre-emptive* and *opt-out* consent models for recruitment to trials evaluating routine treatment effectiveness.

Background

Occurs following participant recruitment, critical care admission, exposure to alert(s) and discharge to ward. Audio transcribed, may take place in person or remotely following discharge from hospital if required. Following completion of follow up interview, participant is discharged from study.

Recap

Before your surgery you kindly agreed to participate in a research study piloting the use of electronic alerts designed to capture and study clinical decision making. The aim of these alerts is to allow clinicians to study routine treatments for which there is little or no pre-existing evidence. We know already that for such treatments, clinicians vary in how they administer these to patients. When clinicians were uncertain about the right treatment decision (given the lack of evidence), the alerts gave them the opportunity to follow the treatment allocated to you through the study, so that we could learn for the future. When clinicians were certain about the best treatment to give, they were allowed to do this, and we recorded what happened in both cases.

Eventually, we hope to develop a system of rapid research studies for routine intensive care treatments that we know vary in how they are applied because of a lack of evidence.

This pilot study has been to see if such a system could work.

Part of the problem with doing research for routine treatments, particularly in intensive care is the difficulty with asking patients for consent to participate in the research study whilst they are very unwell. We wanted to address this problem by asking you to give consent *before* you were admitted to intensive care, back in the Pre-Assessment Clinic. This was possible because we knew

from experience that because of the operation you were having you would come to intensive care after.

The purpose of this interview is two-fold:

1/ To get your thoughts and opinions on giving consent to research before you are admitted to intensive care (what we are calling **pre-emptive** consent).

2/ To get your thoughts on the acceptability of a different way of giving consent, specifically for investigation of routine treatments, which we are calling **opt-out** consent (more on this later).

Semi-Structured Interview Schedule

> Before we start, can I check that you are happy to continue with the interview today?

> It should take approximately 30 minutes.

> I'll be recording what we discuss so that it can be analysed with the rest of the study results after

> As per the Information Sheet, the audio recording will be uploaded to a secure electronic storage vault and won't leave that without being anonymised beforehand.

1. What do you remember about *how* you were asked to provide consent to this study?

    1. Where did it happen?

    2. When did it happen in relation to your operation?

2. Can you remember what the study was investigating? [*this question is used partially to recap in preparation for following questions*]

    1. Alerts

    2. Magnesium

2. Thinking back to when you were asked to consent to this study, how did you feel at the time?

    1. Do you think you understood what the study involved,

        I.e. what it was asking of you as a participant?

    2. Do you think you had the right amount of time to think about the study?

    3. How would you describe your feelings about taking part in a research study?

3. As part of the consent process, you were provided with some written information about the study - what did you think about that?

    1. Was it written clearly?

    2. Were there any parts you did not understand?

4. Throughout the study, were you satisfied that if you wanted to withdraw from the study you knew how to do this?

> One of the advantages of asking for you to consent in clinic, before you are admitted to intensive care, is that we do not have to approach you to consent immediately after your operation.

> Another method used to do research is to conduct the study (with the approval of an ethics committee) and then ask for your consent after it has happened, a process called deferred consent.

> This is often used for studies in intensive care because you may not be able to provide consent at the time as you may be unconscious.

5. Comparing the approach we have taken, to consent you prior to surgery pre-emptively, rather than ask you afterwards, as in deferred consent, which seems more appropriate to you?

6. Overall, having consented to this study using the *pre-emptive* method, do you think it an acceptable method for asking for consent to participate in a research study?

1. Would you find it acceptable to be approached in clinic to participate in further research studies?

7. Do you have any concerns with this method of obtaining consent?

1. Are there circumstances when you think it might be inappropriate or wrong to ask for consent like this?

1. E.g. trying a new or experimental treatment

> I'd like to ask your opinion about another way of giving consent to participate in research, called **opt-out consent**.

> This needs a little explanation.

> For situations where treatments lack evidence, and therefore whether a patient receives them or not is determined by which clinician looks after them (a process which is generally random), we believe it is unethical not to study whether these treatments are effective or not.

> Consider a situation when you are expecting to come into hospital for an operation, and as part of your recovery you will stay on intensive care for a time , as you just have.

> When you receive information about your hospital stay, at the Pre-Assessment Clinic for example, you find it includes a leaflet about intensive care.

> This states that the intensive care unit and the people who work there everyday are committed to continuously learning how they can provide better care for future patients.

> As part of this learning, clinical trials of routinely administered treatments take place on the ICU all the time.

> These trials will never involve the use of new treatments, and will only compare the use of existing treatments within the limits of how they already vary normally.

> The leaflet would explain that the same as all other research, these studies would go through the same rigorous checking and ethical approval as all other clinical trials.

> It would then give you brief information on all the studies currently being conducted.

> It would then ask if you did NOT want to be part of any research during your admission, that you OPT-OUT, via one of several paths (internet, phone contact, discussion with any member of the clinical team).

> If you chose not to opt-out, then you would automatically be enrolled in one of these ongoing research studies as part of your admission.

> You would be able to choose what level of information you would like about the study going forward (updating about the results etc) and you would always have the ability to opt-out at any stage, the same as you had with this study.

8. Were there any elements in that which you did not understand?

9. What do you think of the idea of giving opt-out consent for carefully selected and controlled research studies?

10. If you had received an information leaflet like the one described before your operation this time round what do you think your response would have been?

1. Do you think it would have been acceptable to study a routine treatment, like Magnesium, using this opt-out method of consent?

11. Please review the example leaflet:

1. Are there areas that are unclear?

2. What do you think your response might be?

12. Are there any areas which we have discussed that you feel concerned or worried about?

13. Can you think of any research studies for which opt-out consent would not be appropriate?

1. We would consider any study which investigates a new drug or treatment to be inappropriate for this type of consent.

14. We propose to form a trials committee to evaluate research questions which might potentially be investigated using opt-out consent. We would include patient representatives on this panel. Any research questions which they agree may be appropriate would then go forward to an ethics committee for consideration in the usual way. Are there any additional layers of protection or scrutiny that you would like to see in place?

15. Are you aware of any other research initiatives which use the principle of opt-out consent?

> Thank you for participating in our study - do you have any further questions or anything else you would like to add?

Example Opt Out Leaflet

"Dear Sir/Madam,

> Occasionally patients admitted to hospital require a higher degree of monitoring and care than can be provided on a normal ward.

> This normally means being looked after in the Intensive Care Unit, or ICU, within the hospital.

> At UCLH, we operate an ICU which seeks to use the best modern technology, combined with cutting edge research to continually learn how to improve patient care.

> To do this, we perform lots of research studies on treatments which form the basic routine delivery of Intensive Care.

> These are things like giving Oxygen, giving additional fluids through the vein, or supplementing different salt levels.

> The studies we run on these routine aspects of care are monitored, regulated and approved in the same way as all clinical research studies.

> The aim of the studies is for us to learn how to give future patients better care.

> We investigate these treatments because we know that clinicians may have different strategies when it comes to giving these treatments.

> These differences arise because there is little scientific evidence to guide these decisions.

> When clinicians come to make a decision they know there is limited evidence for, we offer them the opportunity to follow a randomly allocated suggestion that enables us to learn the best strategy for the future.

> The decision about the treatment remains entirely within the control of your doctor or nurse who continue to manage you as they see fit.

> Previous studies we have conducted have shown that most patients are happy for these kinds of routine treatment studies to occur, without asking for consent for each study beforehand.

> In view of this, we operate a system where if you do not want to participate in these studies - you may opt-out of all research activities.

> You can do this by visiting www.uclh.nhs.uk/prospector-optout.com or by discussing opting out with any member of the clinical team.

> You can find a list of all the research studies we are currently conducting at www.uclh.nhs.uk/prospector-criticalcare.com."

SPIRIT Checklist

Item	Description	Reference
1/ Title	Descriptive title identifying the design, population, interventions and acronym	P1
2/ Registration	2a/ Identifier and registry name 2b/ WHO Trial registration data set	P3 (needs completing) ? table/supp materials
3/ Protocol version	Date and version ID	Version 1.0, 22/9/21
4/ Funding	Sources and types of support	P21
5/ Roles and responsibilities	5a/ Names, affiliations and roles of contributors 5b/ Name and contact information for the trial sponsor 5c/ Role of sponsor and funders 5d/ Committees	P21 UCLH/UCL Joint Research Office. uclh.randd@nhs.net 4th Floor, West 250 Euston Road London NW1 2PG Approval and sponsorship of trial protocol. Oversight of trial conduct and data collection. Study Steering Group: Dr Matthew Wilson (PI) Dr Steve Harris (CI) Prof Folkert Asselbergs (Study Advisor) Dr David Brealey (Study Advisor) Prof Matt Sydes (Statistical Advisor) Mr Ruben Miguel (EHRS Analyst)
6/ Background and Rationale	6a/ Research question and justification, summary of existing work 6b/ Choice of comparators	P4 + Main protocol P9
7/ Objectives		P7
8/ Design	Type of trial	P8
9/ Setting	Description of study setting	P8

10/ Eligibility criteria	Incl/Excl criteria	P8
11/ Interventions	11a/ per group description 11b/ stopping criteria 11c/ adherence strategies 11d/ usual care	P9 P9 + main protocol NA P9
12/ Outcomes	Primary & secondary and data	P10-11
13/ Participant timeline	Enrolment, interventions, visits	P16, GANTT in main protocol
14/ Sample size		P11
15/ Recruitment		P8
16/ Allocation	16a/ Sequence generation 16b/ Allocation concealment 16c/ Implementation	P9 NA P9
17/ Blinding	17a/ Who 17b/ Unblinding	NA NA
18/ Data collection	18a/ Collection of outcome, baseline, trial data, data quality 18b/ List of outcome data to be collected for participants who withdraw	P10-11 + main protocol + supp. Materials for interview schedules See consent forms (use data collected up till point of withdrawal)
19/ Data management		P12 + main protocol
20/ Statistical methods	20a/ primary and secondary outcome analysis 20b/ subgroup analyses 20c/ Effect estimate method and missing data handling	P11 + main protocol NA NA
21/ Data monitoring	21a/ Data monitoring committee or explanation of why not needed 21b/ Interim analyses and stopping guidelines	See steering committee and main protocol NA
22/ Harms	Adverse event reporting	Main protocol
23/ Auditing	Frequency and procedures for auditing trial conduct	As per UCL(H) sponsorship guidance.
24/ REC approval		P3 + P12
25/ Protocol amendments	Plans for communicating protocol modifications to relevant parties	Via UCLH Joint Research Office
26/ Consent	26a/ Who will obtain consent and how	P8

	26b/ Additional provisions for participant data collection	Nil additional.
27/ Confidentiality		P12 and main protocol
28/ Declaration of interests		P21
29/ Access to data		P12 and main protocol
30/ Post trial care		Sponsorship and insurance, contact details on Participant information sheets
31/ Dissemination policy	31a/ Communication of results 31b/ Authorship eligibility guidelines and professional writers 31c/ Plans for granting public access to full protocol, participant level dataset and statistical code	P12 NA NA
32/ Informed consent materials	Consent form and PIS	Available on request
33/ Biological specimens		NA

BMJ Open

Embedded Point of Care Randomisation for Evaluating Comparative Effectiveness Questions: PROSPECTOR-Critical Care Feasibility Study Protocol

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Keywords:	STATISTICS & RESEARCH METHODS, Adult intensive & critical care < ANAESTHETICS, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS

Embedded Point of Care Randomisation for Evaluating Comparative Effectiveness Questions: PROSPECTOR-Critical Care Feasibility Study Protocol

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Key Words:

Electronic Health Record Trials; Point of Care Randomisation; Comparative Effectiveness Research; Learning Health Systems

Abstract

Introduction

Many routinely administered treatments lack evidence as to their effectiveness. When treatments lack evidence, patients receive varying care based on the preferences of clinicians. Standard randomised controlled trials are unsuited to comparisons of different routine treatment strategies, and there remains little economic incentive for change.

Integrating clinical trial infrastructure into electronic health record systems offers the potential for routine treatment comparisons at scale, through reduced trial costs. To date, embedded trials have automated data collection, participant identification and eligibility screening, but randomisation and consent remain manual and therefore costly tasks.

This study will investigate the feasibility of using computer prompts to allow flexible randomisation at the point of clinical decision making. It will compare the effectiveness of two prompt designs through the lens of a candidate research question – comparing liberal or restrictive magnesium supplementation practices for critical care patients. It will also explore the acceptability of two consent models for conducting comparative effectiveness research.

Methods and Analysis

We will conduct a single centre, mixed methods feasibility study, aiming to recruit 50 patients undergoing elective surgery requiring postoperative critical care admission. Participants will be randomised to either "Nudge" or "Preference" designs of electronic point-of-care randomisation prompt, and liberal or restrictive magnesium supplementation.

We will judge feasibility through a combination of study outcomes. The primary outcome will be the proportion of prompts displayed resulting in successful randomisation events (compliance with the allocated magnesium strategy). Secondary outcomes will evaluate the acceptability of both prompt designs to clinicians and ascertain the acceptability of pre-emptive and opt out consent models to patients.

Ethics and Dissemination

This study was approved by Riverside Research Ethics Committee (Ref: 21/LO/0785) and will be published on completion.

Registration

This study is sponsored by University College London (Ref: 142382) and registered on ClinicalTrials.gov (Ref: NCT 05149820).

Strengths and Limitations of this Study

- Randomised trials integrated into clinical workflows have shown promise but require further feasibility testing to determine acceptability to patients and clinicians.
- A mixed methods approach allows combination of quantitative outcomes with explanatory qualitative data, increasing understanding of reasons underpinning success or failure of the intervention.
- Testing study feasibility allows estimation of randomisation compliance, judges acceptability of the candidate research question, allows optimisation of electronic prompt design prior to embarking on an adequately powered main trial.
- As the study examines variation at an individual patient and clinician level, it is unclear how generalisable future study results will be outside the study centre.

Introduction

Every day, clinicians collectively make hundreds of thousands of decisions regarding the application of treatments and interventions in the care of patients. Whilst some of these treatments will be guided by robust evidence from Randomised Controlled Trials (RCTs), many "routine" aspects of clinical care continue to lack a strong evidence base [1]. Braithwaite et al describe this as the "60-30-10" challenge – approximately 60% of administered treatments conform to evidence, 30% may be wasted or ineffective, and 10% result in harm [2].

When evidence for an intervention is absent, clinicians vary in their decision making according to their experience and preferences [3]. This variation is manifestly observable and can be seen across multiple domains from choice of surgical procedure [4,5], management of heart failure or diabetic ketoacidosis [6,7], or administration of antibiotics and intravenous fluids [8,9].

Another commonly used treatment which varies in practice is the administration of supplemental magnesium for the prophylaxis of atrial fibrillation in critical care patients. Whilst this practice is commonplace, the only evidence as to its effectiveness comes from the cardiac surgery population [10]. Over time, this has been extrapolated to *all* critical care patients, without additional evidence of benefit. As such, clinicians vary in their threshold for routinely supplementing magnesium. Clinician behaviour will be consistent at extremes of serum magnesium measurements (never/always supplement), but within a "normal" range the decision to supplement will have a random component linked to the clinician's preference [11].

Variation in practice does not necessarily imply substandard care – it may be that the clinician's experience offers benefits in optimising treatment delivery, or it may be that there is no meaningful difference between treatment choices. Under ideal conditions, clinicians would be able to learn from variation and improve the quality and coverage of evidence for future patients. Ineffective yet costly treatments could be minimised, and strategies demonstrating effectiveness targeted to ever small subgroups of patients.

Unfortunately, generating new evidence from routine clinical decision making has proven difficult using existing research methodologies. RCTs are well suited to demonstrating treatment efficacy in homogenised cohorts, under rigid treatment protocols, but have proven costly and difficult to conduct in more pragmatic settings [12]. Whilst the classical RCT remains ideal for evaluating novel therapies, for treatments already in widespread use, with likely small effect sizes, the expense of conducting comparative effectiveness trials becomes untenable. In most cases, researchers rely on observational

methods, which lack the validity derived from prospective randomisation [13]. Therefore, to properly evaluate the comparative effectiveness of multiple treatment strategies, an element of randomisation is essential, together with a mechanism to deploy this efficiently [14].

Electronic Health Record Systems (EHRS) offer a potential solution. Increasingly widespread and comprehensive, they have renewed interest in integrating clinical trials into routine care [15]. Whilst embedding trial infrastructure has improved efficiency, the requirement for point-of-care consent and randomisation remains. Predominantly, this continues to be delivered by a research nurse, partnered with the treating clinician, a process which remains time intensive and financially costly [16].

Two barriers to implementing routine comparative effectiveness research standout – 1) how to fully integrate randomisation into EHRS, ensuring that patient safety and the scientific integrity of the study is maintained; and, 2) what is the correct way for patients to consent to the randomised delivery of routine treatments? Central to these issues is the principle of clinical equipoise – the idea that without evidence, every clinical decision comes with a degree of uncertainty. When the benefits and risks of the treatment are balanced (or unknown), then it becomes justifiable to randomise, in order to learn what decision is best [17,18].

Flexible Electronic Point-Of-Care Randomisation

To learn effectively from clinical decisions, a rapid and responsive randomisation mechanism is required. To achieve this, we propose a two-stage innovation: 1) to embed the randomisation process into the EHRS and link randomisation to the moment of clinical decision making, and 2) to make that randomisation optional for the clinician. The first step ensures the prompt to randomise is presented to the clinician *at the point of potential equipoise*, ensuring relevance and minimising disruption to normal care processes. Step two means the clinician-patient dyad only access the randomisation process if they share equipoise with the trial.

Our design builds on Vickers and Scardino's concept of the clinically-integrated randomised trial, as well as work by Fiore and colleagues in point-of-care trial design [19,20]. To this we add concepts from preference trials, which are designed to explicitly acknowledge treatment preferences to minimise bias [21]. Whilst most of these trials target patient preferences, we believe the concepts are equally applicable to clinicians.

A preference approach has the advantage of allowing clinicians to follow their preferred course of action when they feel strongly, whilst simultaneously allowing randomisation under conditions of equipoise. In this manner, the clinician retains overall responsibility and control over the patient's treatment – ensuring safety is maintained. This is key for integrated trials where, by definition, oversight from research teams is minimised.

We propose to modify existing functionality within the EHRS to intercede at the point of clinical decision making. Many EHRS use Clinical Decision Support Systems (CDSS), based on series of logical rules, to deliver information to clinicians under pre-defined circumstances. These logical rules may be used to emulate inclusion and exclusion criteria within a trial. Once designated conditions are met, an electronic prompt can be displayed to the clinician, at the point of clinical decision making to highlight both the *opportunity* to randomise and the predetermined treatment group *allocation*.

Our design of electronic Point-Of-Care Randomisation (ePOCR) prompt will invite the clinician to consider whether they have equipoise for the treatment decision. In this way, the prompt simply externalises and makes explicit the normal decision-making process.

If the clinician has equipoise, the ePOCR prompt allows them to view the randomised allocation, which can then be followed, and the patient contributes data to the randomised arm of the study. However, if the clinician lacks equipoise, they remain free to follow their preference. In a classical RCT, declining to follow randomisation may represent a protocol violation and result in the participant being excluded from the final analysis. However, in a preference approach, the participant continues to contribute data into the parallel observational study arms determined by the clinician's preference.

Where the clinician declines randomisation, the parallel observational arm of the study continuously evaluates external validity and can identify previously unrecognised subgroups where clinicians have strong preferences that may require modification of the trial. In addition, where preferences are known, these observational arms may be used to identify preference and selection effects, adding extra information to that gained from the treatment effect estimation in the randomised arm [22]. This flexible approach to delivering randomisation is depicted in **Figure 1**.

To integrate randomisation into clinical workflows requires understanding of how clinicians interact with EHRS and how data is used to make decisions. Whilst the use of interruptive prompts based on modified CDSS is an attractive method for accomplishing this, the possible disruption to care processes must be considered. The concept of alert fatigue in this setting is well documented [23]. As such, ePOCR prompts must be designed to be minimally disruptive, whilst permitting the data collection required by the study. To this end, our feasibility study will compare two designs of interruptive

prompt, a simple "Nudge" design, and a more complex "Preference" design. The Nudge prompt encapsulates the simplest version of the study design, whilst the Preference design allows the collection of additional treatment preference data for use in the observational study arm.

Pre-Emptive and Opt-Out Consent

There is ongoing debate as to the most appropriate consent mechanisms for facilitating comparative effectiveness research, specifically, for treatments with demonstrable variation already present in their routine use. Faden and colleagues highlight the strong ethical arguments in favour of streamlining consent procedures in this area and the acceptability to stakeholders of the same [24–27].

In this study we will investigate moving the point at which consent is obtained proximally, away from the final application of eligibility criteria and randomisation. A future model might see patients routinely consented for a range of potential trials (under a specific operational framework such as that suggested by Fiore and Lavori [14]) on admission to hospital, before it is known whether or not they will be eligible. This single point of contact would decrease the burden of identifying and consenting patients and minimise disruption to clinical workflows.

Study Objectives

The overall study aim is to ascertain the feasibility of conducting a future clinical trial using infrastructure integrated into the EHRS and using a system of ePOCR. Feasibility will be judged by combining outcome data related to 1) the effectiveness of the ePOCR system and, 2) the acceptability of ePOCR to clinicians. Since the feasibility of scaling future large scale trials using ePOCR and preference design approaches is reliant on a streamlined consent model, we will also evaluate the acceptability of both pre-emptive and opt-out consent models to patients. Finally, we will collect pilot data specific to the candidate research question of magnesium supplementation to inform design of a future trial.

Methods and Analysis

Study Design and Setting

This single centre, mixed methods feasibility study will follow an explanatory-sequential design, which allows supplementation of quantitative data on the effectiveness of ePOCR with qualitative data to aid interpretation [28]. The study will run across four critical care units within University College London Hospitals (UCLH) NHS Trust from January to August 2022. These critical care units care for a mix of surgical patients including colorectal, urology and thoracics but excluding cardiac and neurosurgery. UCLH has used the Epic EHRS since 2018.

We will recruit patients aged 18 years and over, undergoing elective surgery of sufficient complexity to warrant postoperative admission to critical care. This cohort was selected opportunistically to facilitate obtaining informed consent *pre-emptively* during hospital visits prior to surgery. Potentially eligible participants will be identified through a combination of algorithmic screening of the EHRS by surgical procedure code, and by manual identification from booked critical care admissions.

We will recruit a cohort of critical care clinicians to undertake the qualitative interview program. The intervention is targeted to bedside critical care nurses. There are approximately 300 critical care nurses working across all the study sites. Neither clinicians nor patients will be compensated for participating in the study.

Exclusion criteria will be applied at two stages. Patients unable to provide written informed consent, or who are pregnant will be excluded. Following postoperative admission to critical care, patients whose initial documented heart rhythm is atrial fibrillation will be excluded. Prior to the deployment of the ePOCR prompt, the EHRS will screen against the following criteria: 1) no documented allergy or intolerance to any preparation of supplemental magnesium, 2) no active treatment for bronchospasm (defined as active treatment administration indicating bronchospasm and screening of active problem list), and 3) the most recent serum magnesium result prior to prompt deployment lies between 0.5 and 1.5 mmol/L. This final criterion ensures that the prompt does not facilitate randomisation for magnesium values outside the scope of reasonable clinical equipoise. For example, serum magnesium values < 0.5 mmol/L would normally always be supplemented, and vice versa for values > 1.5 mmol/L.

Upon successful conclusion of the screening process, the ePOCR prompt will display to the bedside critical care nurse. The screening process repeats for each new serum magnesium result received. Screening and overall participant flow through the study are illustrated in **Figure 2**.

Qualitative assessments will be conducted in three stages. A random sample of all critical care clinicians involved in routinely caring for this patient cohort will be invited to undertake an initial interview. Two further interviews focus specifically on the bedside critical care nurses exposed to the ePOCR prompts.

Patient and Public Involvement

We sought opportunities to engage with patients and the public from study inception. To this end, two focus groups were conducted. The first addressed utilisation of electronic clinical data for research and the presence of naturally occurring variation in practice for evidence-light treatments. The second focused on the premise of flexible ePOCR and the need to investigate alternative consent models for comparative effectiveness research. These groups highlighted a general lack of awareness regarding evidence gaps for routine treatments. Both groups agreed this is a priority area for future research. The authors are grateful to members of both groups for their feedback in improving the clarity of communication regarding a complex study design. We plan to disseminate study results to consenting participants on completion.

Interventions

Electronic Point-Of-Care Randomisation Prompts

This study will compare two ePOCR prompts – Nudge versus Preference designs, illustrated in **Figure 3**. The Nudge design is characterised by its passive nature and requires minimal interaction from the clinician. The intention is to 'nudge' the clinician to consider their level of equipoise for the decision to supplement magnesium and follow the randomised treatment where they have no preference. In contrast, the Preference design facilitates the explicit recording of the clinician's treatment preference, whilst simultaneously allowing randomisation under conditions of equipoise. Preference

options are presented as three possible choices – a strong preference for or against administering supplemental magnesium, and no preference. If no preference is selected, the randomised action is provided. If the clinician selects a strong preference, they are advised to continue with their preferred treatment. Whilst this design is more burdensome because it requires interaction, it will allow the derivation of preference and selection effects as described above.

Both prompt designs will be constructed using the Epic build module designed for 'Best Practice Advisory' creation, essentially a form of clinical decision support. Construction of a system of logical rules will allow screening of eligibility criteria as described. The technical aspects of both prompt designs will be tested in a sandbox environment prior to live deployment.

Deployment follows the same pathway for both ePOCR prompt designs. Following recruitment participants will be randomised to either Nudge or Preference design. They will then be randomised again to either liberal or restrictive magnesium supplementation strategies (**Figure 4**). The liberal magnesium arm will encourage supplementation at a serum magnesium value < 1.0 mmol/L. The restrictive arm will encourage supplementation at a serum magnesium value < 0.75 mmol/L. These values were determined from an observational study of supplementation practices at the study centre and fall within the boundaries of observed variation in practice [11].

Randomisation will be conducted using the EHRS, which conducts simple randomisation using an internal number rule [29]. For this feasibility study, basic randomisation without additional covariate balancing will be used. Randomisation will remain the same for both prompt design and magnesium strategy throughout study participation.

Both prompts will display to the bedside critical care nurse under either of two conditions: 1) accessing of the participant's blood test results, or 2) accessing the supplemental magnesium prescription within the EHRS. The prompt will deploy once for each new serum magnesium result, for five postoperative days or the end of the participant's critical care admission, whichever is sooner.

This study has been designed to be highly pragmatic. At our institution it is normal practice for all patients admitted to critical care to be issued with an "as required" prescription for either intravenous or oral magnesium. In both study arms, the method and frequency of magnesium supplementation, and frequency of serum magnesium measurement remain at the discretion of the clinical team.

Qualitative Assessments

Both clinician and patient interviews follow a semi-structured design. Prior to ePOCR deployment, critical care clinicians will be invited to undertake an interview exploring general attitudes towards EHRS research and their current interactions with existing electronic alerts. The interview will feature guided simulation introducing both prompt designs and encouraging initial feedback. The use of simulation to introduce the prompts acknowledges the logistical difficulty in ensuring that each critical care nurse participating in the study is exposed to each prompt design at least once during the study period.

Critical care nurses will undertake a further interview following exposure to an ePOCR prompt to gather immediate feedback. A final follow up interview will invite nurses to give a preference on prompt design, having experienced the intervention in a clinical setting.

Patients participating in the study will undertake a semi-structured interview following discharge from critical care. This will explore attitudes towards pre-emptive and opt-out consent models. Interview schedules are included in **Supplementary Materials S1**.

Outcomes, Data Collection & Analysis

We will collect descriptive data on ePOCR performance. The primary study outcome will be the proportion of prompts of either design which result in compliance with randomisation by the clinician. Estimates of prompt compliance will be generated for both liberal and restrictive magnesium strategies in addition. Compliance is defined as either: 1) the appropriate administration of magnesium following prompt deployment, where the measured serum magnesium is less than the randomised threshold; or, 2) the appropriate withholding of supplemental magnesium following prompt deployment, where the serum magnesium is greater than the randomised threshold. The potential outcomes following prompt deployment are illustrated in **Figure 5**, using the Nudge design as an example.

For the Preference design, descriptive data will be presented across the range of possible responses. We will link events where the clinician declines randomisation and expresses a strong preference to the subsequent action (administration of magnesium or not). The observation period for assessing

compliance will be defined as the time from exposure to prompt to the subsequent shift change in clinical team. We will assess between group differences in proportion using a Chi-squared test.

All quantitative data pertinent to addressing the study outcomes will be extracted from the EHRS. The study will not require any additional documentation or data entry by clinical teams. We will extract routinely collected clinical data from the EHRS for study patients to aid planning a future main study. This will include baseline rates of atrial fibrillation in the study population, frequency of serum magnesium measurement, frequency of supplementation and estimates of treatment group separation (difference in mean serum magnesium values between liberal and restrictive groups).

The semi-structured interview program will contribute qualitative data to both primary and secondary outcomes. Overall study feasibility will be judged through a combination of ePOCR prompt compliance rates and acceptability to clinicians. ePOCR compliance data will contribute to further simulation work designed to estimate plausible ranges of samples sizes for a main study, which will be used to further demonstrate study design feasibility.

We will use a thematic analysis approach to analyse interview data as described by Braun and Clarke and illustrated in a recent analysis by McNulty et al [30,31].

The primary objective of the study is to determine the feasibility of using ePOCR prompts. Overall feasibility will be judged using technical aspects around design and implementation and the experience of clinicians, which will both be assessed qualitatively.

Whilst overall study feasibility will be contingent on the rate of prompt compliance (the proportion of alerts where the clinician complies with randomisation), we will also estimate differences in compliance between nudge and preference designs to add to our qualitative assessments. We propose a non-inferiority approach based on the premise that the preference design has improved research utility relative to the nudge design through estimation of treatment and selection effects. Therefore, if the preference prompt proves non-inferior in terms of observed compliance, and qualitatively acceptable, it would be demonstrably the preferred design. We will not seek to test between group differences for each magnesium strategy in addition.

To this end we estimate the required sample size based on hypothesised equal compliance rate of 50% in both groups. We hypothesise a non-inferiority margin of -25% to be justifiable relative to the additional data the preference design would provide. This produces a sample size of 50 prompts per design, with a power of 80% and a 5% significance level [32]. Using an average of two prompts per patient, this results in a sample size of 25 patients per group.

We will aim to recruit 20 clinicians identified as key informants relevant to the study question to undertake baseline interviews [33]. We will employ a purposive sampling strategy as used by Connell et al to evaluate a complex digital intervention in a similar healthcare setting and justified by international consensus guidance for mixed-methods research [34,35]. We will aim to interview all bedside nurses who receive a prompt and use guided simulation to aid the evaluation of preference for either prompt design.

Ethics and Dissemination

This study protocol was approved by the NHS Riverside Research Ethics Committee (Ref: 21/LO/0785) and sponsored by University College London (Ref: 142382).

Potentially eligible patients will be approached during their anaesthetic pre-assessment clinic visit. After confirming initial eligibility, a member of the research team will discuss the study and issue the Participant Information Sheet (**Supplementary Materials S2**), which includes research team contact information and mechanisms to withdraw from the study at any point. The patient will be able to give written consent (**Supplementary Materials S3**) at any point from initial approach to immediately prior to surgery.

By approaching patients in pre-assessment clinic, we evaluate a pre-emptive approach to providing consent which may be transitioned to an opt-out approach in the future if acceptable. We justify obtaining consent at the initial visit in three ways. Firstly, the study premise and intervention carry minimal risk to the participant, secondly, the burden on the participant is low (one follow-up interview following surgery). Thirdly, we provide multiple routes to discontinue participation with multiple checks throughout the perioperative journey.

We ensure participant data is protected by extracting on data pertinent to the study from the EHRS. All clinical data obtained during the study will remain within UCLH computer infrastructure and firewall. Data extracted from the EHRS will only be accessible by designated members of the research team and presented as summary level data. Interview data will be audio recorded and uploaded via secure email to UCLH computer systems for analysis. Only anonymised quotes will be utilised in the study reports. We plan to disseminate results by publication in peer-reviewed journals and will also prepare reports for patients and clinicians involved in the study upon completion.

Author Contributions

SKH, FWA and MGW conceived the research idea and developed the study design. SKH is the chief investigator for the study and MGW the principal investigator. MGW prepared the initial manuscript, and all authors were involved in contributing major edits. RM & MGW designed the ePOCR prompt system. DB assisted with trial design, implementation, clinical oversight, and manuscript review. All authors have read and approved the final protocol and this manuscript.

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Competing Interests

The authors declare that they have no conflict of interest.

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Data Sharing Statement

Summaries of data analysis from the feasibility study will be available upon request.

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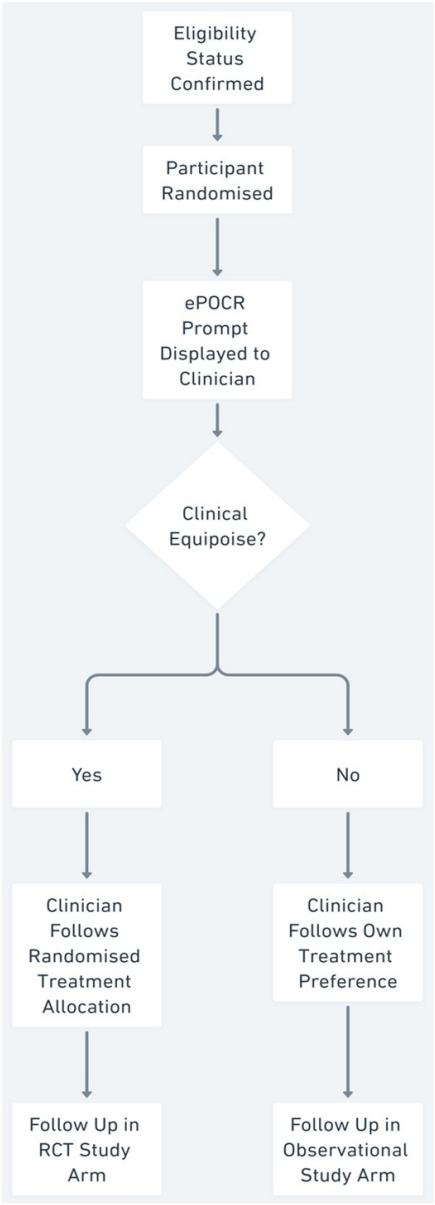
Figure 1 – Flexible Randomisation as an Expression of Clinical Equipoise

Figure 2 – Anticipated Participant Flow Through Study

Figure 3 – Two Stage Randomisation Process

Figure 4 – Examples of Nudge (top) and Preference (bottom) ePOCR prompt designs

Figure 5 – Derivation of Compliance with Randomisation from Observed Clinician Action



Flexible Randomisation as an Expression of Clinical Equipoise

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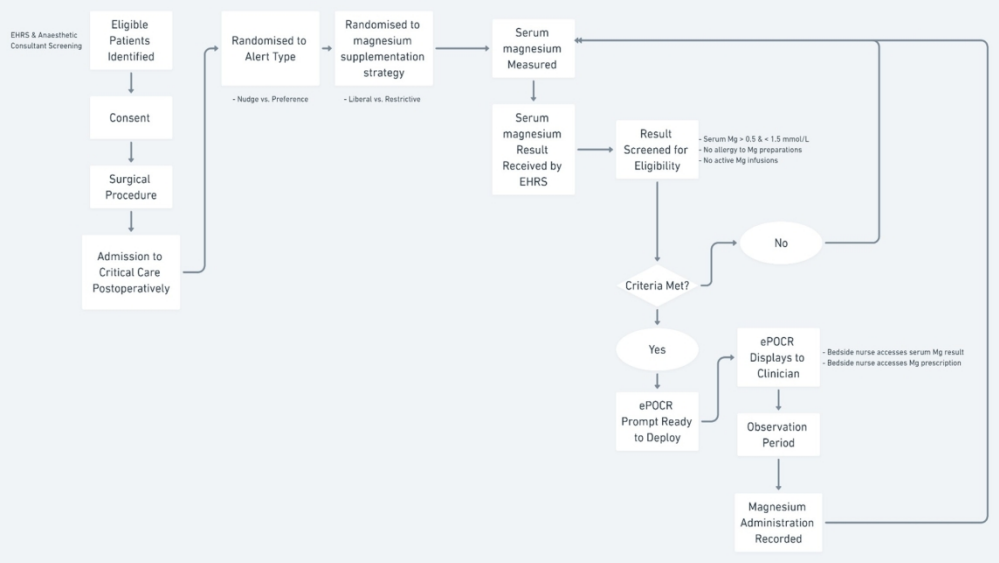

Anticipated Participant Flow Through Study

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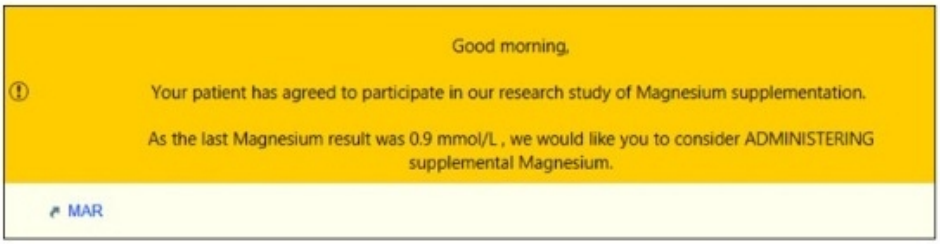

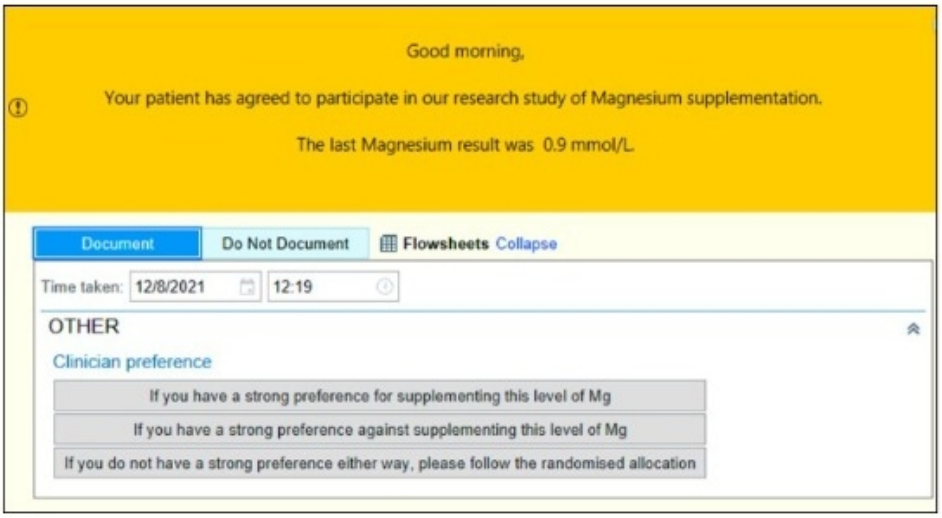

Two Stage Randomisation Process

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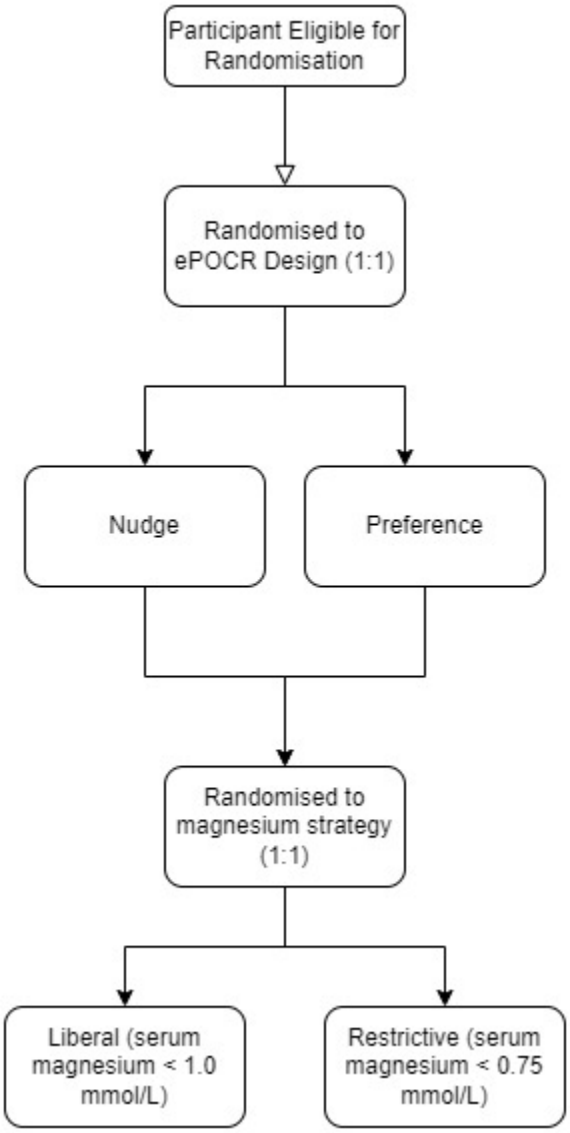
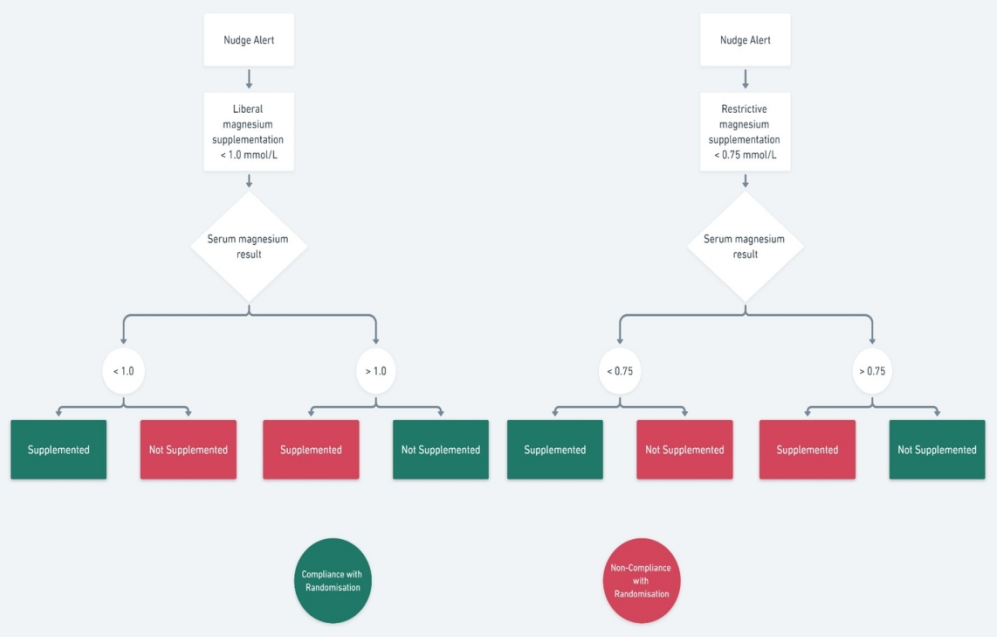


Examples of Nudge (top) and Preference (bottom) ePOCR prompt designs

106x204mm (72 x 72 DPI)



Derivation of Compliance with Randomisation from Observed Clinician Action

204x130mm (220 x 220 DPI)

Supplementary Materials

S1 Clinician & Patient Semi-Structured Interview Schedules

IRAS ID: 279737

Centre Number: 1

Study Number: 142382

Version Number: 1.0 (22.09.21)

PROSPECTOR-Critical Care - Clinician Interview Schedule

Design

Following recruitment, clinicians will be asked to participate in a three-stage interview process. The first interview will be open to all critical care clinicians. The remaining two interviews will focus on critical care nurses who interacted with the prompts during the intervention phase.

Pre-Intervention Interview

This will collect background information on the individual nurse, including seniority and critical care experience and interactions with clinical research and electronic health record systems, including Best Practice Alerts specifically. The nurse will be asked about their understanding of their current practices regarding supplementing Mg, drivers, and motivators for administration and specific questions to elicit their perceived zone of equipoise for administering Mg based on serum Mg levels.

After gathering baseline information, each clinician will undertake a guided simulation of each alert design as a demonstration. Following the simulation, participants will be asked for feedback on the alert principles and design aspects.

Post-Exposure Interview

Specifically directed at the critical care nurses interacting with the alert, this interview will take place following exposure to the alert, within the intervention phase of the study. It will focus on areas such

as usability, understanding and impact on the individual's clinical workflow. It will focus on highlighting reasons for compliance or defiance with the alert.

Follow-Up Interview

Following completion of the intervention phase, clinicians who were exposed to the alert will be invited to undertake a follow up interview. The purpose of this is to explore their overall attitudes towards the study and to garner qualitative comparison data on the two alert designs. It is likely that the majority of the participating nurse cohort will only be exposed to one of the two alert designs during the intervention period due to the scale of the study. To enable a comparison to be made, participants will be invited to review the simulation of the alert they did not interact with clinically during the interview. The use of simulated alerts for comparison will be recorded. The subgroup of nurses interacting with both alerts during the intervention phase will be presented in the results.

Pre-Intervention Interview

Aims

- Gather baseline information about clinicians

- Baseline qualitative data on attitudes towards Magnesium supplementation

- Guided simulation of both types of alert

- First-impression feedback on alert principles and design

Background

- Occurs following participant recruitment (nurses) or in isolation for other ICU clinicians.

    - Following review of Participant Information Sheet and Consent Form.

- Audio transcribed, simulation guided using Epic.

- Following interview completion, nurses will continue on to the intervention phase of the study, other ICU clinicians will complete study.

- Anticipated duration: 30 minutes

Semi-Structured Interview Schedule

> Before we start, can I check that you are happy to continue with the interview today?

> It should take approximately 30 minutes

> I'll be recording what we discuss so that it can be analysed with the rest of the study results after

> As per the Information Sheet, the audio recording will be uploaded to a secure electronic storage vault and won't leave that without being anonymised beforehand.

1. **What is your role in the ICU?**
    - **a.** If ICU nurse:
        - **i.** Number of years qualified.
        - **ii.** Number of years working in critical care.
        - **iii.** Banding.
        - **iv.** Duration worked in this ICU.
        - **v.** Number of shifts per week.
2. **Have you been involved in research studies for critical care patients before?**
    - **a.** Which ones?
    - **b.** What was your role?
    - **c.** Have you been involved in any research studies using Epic?
3. **Thinking about the routine treatments that we give to critical care patients daily, can you estimate the proportion of these that are underpinned by good quality evidence?**
    - **a.** How do you interact with evidence about the treatments you give?
        - **i.** Journals
        - **ii.** Clinical guidelines
        - **iii.** MDT/Teaching/Colleagues
4. **How do you interact with a patient's blood test results?**
    - **a.** Do you review them yourself (i.e. independently of the ward round for nurses).
    - **b.** Do you review them every shift?
    - **c.** How does reviewing blood tests integrate into your daily workflow?
        - **i.** Is there a particular time during each shift where you review them?
        - **ii.** Would you review them on a night shift?
        - **iii.** What kind of actions do you take from reviewing the blood test results?
5. **What are the main reasons you might administer supplemental Magnesium to a critical care patient?**
    - **a.** Clinical indications
    - **b.** What drives you to access the PRN Magnesium prescription?
6. **How often would you administer (or request) supplemental Magnesium?**
    - **a.** What proportion of your shifts?
    - **b.** What proportion of your patients?
7. **Do you ever consult anyone else about whether or not to give supplemental Magnesium?**
    - **a.** Who?
    - **b.** How often?
8. **Consider a patient's serum Magnesium lab result – do you have a threshold for giving Magnesium?**
    - **a.** Low (when you would always give)
    - **b.** High (when you would never give)
    - **c.** How would you decide what to do in between these values?
9. **Do you ever feel uncertain about what level of Magnesium to supplement at?**
    - **a.** Can you estimate the numbers around which you feel uncertain?

b. What makes you uncertain?
c. What do you do if you are not sure what to do?

10. What are your feelings about Epic as an Electronic Health Record System?

11. Do you interact with any pop-up alerts at the moment?

a. Which ones?
b. What do you think of them?
c. Do they ever prompt you to change your clinical practice?

> I'd like to show you two designs of electronic alert.

> These are designed to activate within Epic, under specific conditions - in this case, around the time that the ICU nurse is reviewing blood test results or considering administering supplemental Magnesium.

> I'll walk you through how the alerts activate, and how you might interact with them and then ask what you think about them.

> Walk through Nudge Alert.

> Walk through Preference Alert.

12. What are your initial thoughts about these two alerts?

13. Can you describe what the alert is asking you to do?

14. What do you think your response to the alerts might be?

a. For non-nurses, ask them to consider a similar research question relevant to their role to frame the question in more relevant terms.

15. Do you think these alerts will be disruptive to your clinical workflow?

Post-Exposure Interview

Aims

- Assess alert useability and understanding of the alert.
- Assess immediate feedback on clinical workflow impact.
- Assess reasons for compliance or defiance with alert.

Background

This interview is focused on critical care nurses who have interacted with one of the alert designs in a clinical setting. It is designed to be carried out within the same shift as the nurse receives the exposure. Intended duration: 15 minutes.

Semi-Structured Interview Schedule

1. **Did you receive any electronic alerts whilst looking after your patient today?**
    a. What were they?
    b. What were you doing when you received them?
2. **How did you feel when you received the Magnesium alert?**
3. **What was the Magnesium alert asking you to do?**
4. **Did you follow the suggestion of the alert?**
    a. Why?
    b. Did you feel that the alert was clear in what it was asking of you?
    c. Did you feel pressured to do something you weren't comfortable with?
5. **Thinking back to what you were doing when you received the alert: how did you feel about the timing of the alert activating?**
    a. Was it inconvenient? How would you fix it?
    b. Did you feel you had enough time to review it and consider what to do?
    c. Currently the alert deploys based on when you look at the blood test results or when you access the Magnesium prescription, can you think of better times or triggers for the alert to activate which might work better with your workflow?
6. **What did you do immediately following the alert?**
7. **How do you feel about how frequently the alert popped up?**
8. **What do you think of the design of the alert itself?**
    a. Easy to understand? // Unclear language? // Too much or too little information?
9. **Did you discuss the alert/decision to give Magnesium with any other members of the clinical team?**
10. **How do you think this alert impacted or changed the patient's care?**
11. **If the patient was able to, did you discuss the alert or decision to supplement Magnesium with the patient?**
12. **Would you routinely discuss Magnesium supplementation at handover?**

Follow Up Interview

Aims

- Explore overall attitudes towards the study.
- Compare and contrast alert designs and elicit preferences.

Background

This interview will be conducted following conclusion of the intervention phase and will be focused on participating critical care nurses who were exposed to an alert whilst delivering clinical care.

It is anticipated that nurses may not be exposed to both alert designs during the intervention period and as such this interview will include a second simulated walk through of the alert design not seen clinically to facilitate a comparison. Intended duration: 30 minutes.

Semi-Structured Interview Schedule

1. **During the course of looking after patients in this study, were you exposed to an electronic alert about Magnesium?**
    a. How many times did you receive the Magnesium alert in total?
2. **Were you exposed to two types of alert design at least once?**
    a. Show picture examples to aid recall.
    b. Can also compare against exposures from EHRS.

> At this point, if the nurse has not been exposed to one type of alert design, pause the interview and go back through the simulated walk through for the alternative alert type as a refresher.

3. **If you compare both designs of the alert, do you prefer one design over the other?**
    a. Why?
    b. What are the good and bad aspects of each design?
4. **Do you feel that one type of alert made you more likely to follow the randomised allocation over the other?**
5. **Do you think you were more likely to ignore one design over the other?**
6. **Overall, how have you found taking part in this study?**
7. **What do you think about the potential for using alerts like this to research routine treatments in ICU?**
8. **If we ran a larger scale version of this trial, with the aim of finding out if liberal or restrictive Magnesium supplementation was better at preventing Atrial Fibrillation:**
    a. Would you take part?
    b. Which alert would you pick to use?
    c. What do you think the result of the trial would be?

9. **Imagine we were using this design of experiment (with electronic alerts and randomisation) to investigate different ICU treatments at the same time. This means that you might get more than one alert for different treatments during a shift:**
    a. What do you think about having more than one alert question running at once?
    b. What do you think the maximum number of different alerts that would be tolerable is?
10. **Part of the process for picking research questions to investigate with this method is that we demonstrate a lack of evidence as to the best course of action, and existing variation in how clinicians administer the treatment. Consider each of these scenarios, would you be happy to use the alert randomisation method to investigate them?**
    a. Randomising to different durations of postoperative antibiotic treatment to prevent surgical site infections.
    b. Randomising to different thresholds of Haemoglobin at which to "top-up" with a blood transfusion.
    c. Randomising to different thresholds of temperature at which to administer Paracetamol for a fever.
    d. Randomising to different target mean arterial blood pressures for patients.
    e. Randomising to different durations of non-invasive ventilation before intubation for patients with pneumonia.

IRAS ID: 279737

Centre Number: 1

Study Number: 142382

Version Number: 1.0 (22.09.21)

PROSPECTOR-Critical Care - Patient Interview Outline

Aims

Evaluate acceptability of *pre-emptive* and *opt-out* consent models for recruitment to trials evaluating routine treatment effectiveness.

Background

Occurs following participant recruitment, critical care admission, exposure to alert(s) and discharge to ward. Audio transcribed, may take place in person or remotely following discharge from hospital if required. Following completion of follow up interview, participant is discharged from study.

Recap

Before your surgery you kindly agreed to participate in a research study piloting the use of electronic alerts designed to capture and study clinical decision making. The aim of these alerts is to allow clinicians to study routine treatments for which there is little or no pre-existing evidence. We know already that for such treatments, clinicians vary in how they administer these to patients. When clinicians were uncertain about the right treatment decision (given the lack of evidence), the alerts gave them the opportunity to follow the treatment allocated to you through the study, so that we could learn for the future. When clinicians were certain about the best treatment to give, they were allowed to do this, and we recorded what happened in both cases.

Eventually, we hope to develop a system of rapid research studies for routine intensive care treatments that we know vary in how they are applied because of a lack of evidence.

This pilot study has been to see if such a system could work.

Part of the problem with doing research for routine treatments, particularly in intensive care is the difficulty with asking patients for consent to participate in the research study whilst they are very unwell. We wanted to address this problem by asking you to give consent *before* you were admitted to intensive care, back in the Pre-Assessment Clinic. This was possible because we knew

from experience that because of the operation you were having you would come to intensive care after.

The purpose of this interview is two-fold:

1/ To get your thoughts and opinions on giving consent to research before you are admitted to intensive care (what we are calling **pre-emptive** consent).

2/ To get your thoughts on the acceptability of a different way of giving consent, specifically for investigation of routine treatments, which we are calling **opt-out** consent (more on this later).

Semi-Structured Interview Schedule

> Before we start, can I check that you are happy to continue with the interview today?

> It should take approximately 30 minutes.

> I'll be recording what we discuss so that it can be analysed with the rest of the study results after

> As per the Information Sheet, the audio recording will be uploaded to a secure electronic storage vault and won't leave that without being anonymised beforehand.

1. What do you remember about *how* you were asked to provide consent to this study?

    1. Where did it happen?

    2. When did it happen in relation to your operation?

2. Can you remember what the study was investigating? [*this question is used partially to recap in preparation for following questions*]

    1. Alerts

    2. Magnesium

2. Thinking back to when you were asked to consent to this study, how did you feel at the time?

    1. Do you think you understood what the study involved,

        I.e. what it was asking of you as a participant?

    2. Do you think you had the right amount of time to think about the study?

    3. How would you describe your feelings about taking part in a research study?

3. As part of the consent process, you were provided with some written information about the study - what did you think about that?

    1. Was it written clearly?

    2. Were there any parts you did not understand?

4. Throughout the study, were you satisfied that if you wanted to withdraw from the study you knew how to do this?

> One of the advantages of asking for you to consent in clinic, before you are admitted to intensive care, is that we do not have to approach you to consent immediately after your operation.

> Another method used to do research is to conduct the study (with the approval of an ethics committee) and then ask for your consent after it has happened, a process called deferred consent.

> This is often used for studies in intensive care because you may not be able to provide consent at the time as you may be unconscious.

5. Comparing the approach we have taken, to consent you prior to surgery pre-emptively, rather than ask you afterwards, as in deferred consent, which seems more appropriate to you?

6. Overall, having consented to this study using the *pre-emptive* method, do you think it an acceptable method for asking for consent to participate in a research study?

1. Would you find it acceptable to be approached in clinic to participate in further research studies?

7. Do you have any concerns with this method of obtaining consent?

1. Are there circumstances when you think it might be inappropriate or wrong to ask for consent like this?

1. E.g. trying a new or experimental treatment

> I'd like to ask your opinion about another way of giving consent to participate in research, called **opt-out consent**.

> This needs a little explanation.

> For situations where treatments lack evidence, and therefore whether a patient receives them or not is determined by which clinician looks after them (a process which is generally random), we believe it is unethical not to study whether these treatments are effective or not.

> Consider a situation when you are expecting to come into hospital for an operation, and as part of your recovery you will stay on intensive care for a time , as you just have.

> When you receive information about your hospital stay, at the Pre-Assessment Clinic for example, you find it includes a leaflet about intensive care.

> This states that the intensive care unit and the people who work there everyday are committed to continuously learning how they can provide better care for future patients.

> As part of this learning, clinical trials of routinely administered treatments take place on the ICU all the time.

> These trials will never involve the use of new treatments, and will only compare the use of existing treatments within the limits of how they already vary normally.

> The leaflet would explain that the same as all other research, these studies would go through the same rigorous checking and ethical approval as all other clinical trials.

> It would then give you brief information on all the studies currently being conducted.

> It would then ask if you did NOT want to be part of any research during your admission, that you OPT-OUT, via one of several paths (internet, phone contact, discussion with any member of the clinical team).

> If you chose not to opt-out, then you would automatically be enrolled in one of these ongoing research studies as part of your admission.

> You would be able to choose what level of information you would like about the study going forward (updating about the results etc) and you would always have the ability to opt-out at any stage, the same as you had with this study.

8. Were there any elements in that which you did not understand?

9. What do you think of the idea of giving opt-out consent for carefully selected and controlled research studies?

10. If you had received an information leaflet like the one described before your operation this time round what do you think your response would have been?

1. Do you think it would have been acceptable to study a routine treatment, like Magnesium, using this opt-out method of consent?

11. Please review the example leaflet:

1. Are there areas that are unclear?

2. What do you think your response might be?

12. Are there any areas which we have discussed that you feel concerned or worried about?

13. Can you think of any research studies for which opt-out consent would not be appropriate?

1. We would consider any study which investigates a new drug or treatment to be inappropriate for this type of consent.

14. We propose to form a trials committee to evaluate research questions which might potentially be investigated using opt-out consent. We would include patient representatives on this panel. Any research questions which they agree may be appropriate would then go forward to an ethics committee for consideration in the usual way. Are there any additional layers of protection or scrutiny that you would like to see in place?

15. Are you aware of any other research initiatives which use the principle of opt-out consent?

> Thank you for participating in our study - do you have any further questions or anything else you would like to add?

Example Opt Out Leaflet

"Dear Sir/Madam,

> Occasionally patients admitted to hospital require a higher degree of monitoring and care than can be provided on a normal ward.

> This normally means being looked after in the Intensive Care Unit, or ICU, within the hospital.

> At UCLH, we operate an ICU which seeks to use the best modern technology, combined with cutting edge research to continually learn how to improve patient care.

> To do this, we perform lots of research studies on treatments which form the basic routine delivery of Intensive Care.

> These are things like giving Oxygen, giving additional fluids through the vein, or supplementing different salt levels.

> The studies we run on these routine aspects of care are monitored, regulated and approved in the same way as all clinical research studies.

> The aim of the studies is for us to learn how to give future patients better care.

> We investigate these treatments because we know that clinicians may have different strategies when it comes to giving these treatments.

> These differences arise because there is little scientific evidence to guide these decisions.

> When clinicians come to make a decision they know there is limited evidence for, we offer them the opportunity to follow a randomly allocated suggestion that enables us to learn the best strategy for the future.

> The decision about the treatment remains entirely within the control of your doctor or nurse who continue to manage you as they see fit.

> Previous studies we have conducted have shown that most patients are happy for these kinds of routine treatment studies to occur, without asking for consent for each study beforehand.

> In view of this, we operate a system where if you do not want to participate in these studies - you may opt-out of all research activities.

> You can do this by visiting www.uclh.nhs.uk/prospector-optout.com or by discussing opting out with any member of the clinical team.

> You can find a list of all the research studies we are currently conducting at www.uclh.nhs.uk/prospector-criticalcare.com."

S2 – Patient Information Sheet

University College London Hospitals NHS
NHS Foundation Trust

Participant Information Sheet (Patients)

Study Title:

Feasibility Study of **PROSPECTOR** – ***P****oint of care* ***R****and****O****misation* ***S****ystems for* ***P****erforming* ***E****mbedded* ***C****omparative effectiveness* ***T****rials* ***O****f* ***R****outine treatments in Critical Care*

Protocol Number: 1.0 (22.09.21)

Sponsor: University College London, *this study is being conducted as part of a PhD study program*

Principle Investigator: Dr. Matthew Wilson

Site: *University College London Hospitals NHS Trust*

Version: 1.1 (05.11.21)

Invitation

We would like to invite you to take part in our research study. Before you decide to participate, it is important that you understand why the research is being done and what it would involve for you. One of the research team will go through this information sheet with you, to help you decide if you would like to take part and to answer any questions you may have. This should take about 10 minutes. Please feel free to talk to others about the study if you wish.

Background to the Study

During a hospital stay, some patients require additional care that cannot be provided on a ward. In these cases, patients come to the Intensive Care Unit and receive close monitoring and nursing care. For some operations, patients will routinely come to Intensive Care immediately after surgery.

Every day, doctors and nurses working in Intensive Care make hundreds of decisions about treatments - like when to start or stop them, or how frequently to give them. Ideally, decisions are based on gold standard evidence from scientific studies known as Randomised Controlled Trials (RCTs). Unfortunately, for many commonly used treatments, little or no evidence about how best to use them exists, and clinicians must use knowledge and experience to decide what is best.

As clinicians are all different, this can mean that patients can receive different treatments depending on who looks after them. For example, magnesium is routinely given to patients in Intensive Care to

prevent abnormal heart rhythms. There is no evidence supporting this practice and clinicians vary in how they give magnesium to patients.

Whilst a standard clinical trial might be run to answer the question of how best to give magnesium, this method is very expensive and labour-intensive as research teams must conduct tasks such as randomly allocating patients to treatments manually (known as randomisation).

Increasingly, we are using hospital computer systems to make conducting clinical trials less costly and more efficient by automating some of the required processes. These computer systems also possess mechanisms for prompting and guiding clinicians for certain decisions, reminding them of best practices, or warning them of potential problems. These systems may be modified to allow clinicians to follow a treatment allocated randomly, within the boundaries of a clinical trial. If successful, this will help us generate evidence for how best to give these treatments to patients.

In this study we will investigate whether electronic computer prompts can be used to allow clinicians to follow a randomly allocated strategy for administering magnesium in the Intensive Care Unit.

What is the Aim of the Study?

This is a feasibility study, designed to find out how doctors and nurses might respond to two different designs of computer prompt designed to enable them to follow a magnesium treatment strategy, under conditions where they would normally be uncertain as to the best strategy.

In addition, we would like to obtain your thoughts on different methods of providing informed consent to participate in this kind of research into routine care practices. This would be done by interview at the end of the study.

What Intervention is being examined?

This study will compare two designs of computer prompt. These will be displayed to the Intensive Care nurses at the time they make the decision about whether to give extra magnesium or not. The prompts will ask the nurse to consider how strongly they feel about giving or not giving magnesium. If the nurse feels strongly that giving or not giving magnesium is the correct decision, they will follow their treatment preference. However, if the nurse has no strong feelings either way, they will be encouraged to follow the magnesium strategy allocated by the study, and displayed on the prompt. This will enable the study to learn about what kind of magnesium strategy is best, whilst ensuring that clinicians retain control over what treatments patients receive.

We also wish to gather the views of patients like yourself on different ways of asking for your consent to participate in research studies, specifically for treatments in hospital which form part of routine care, but which lack good evidence as to their effectiveness.

Why am I being asked to participate in this study?

You are scheduled to have an operation which would normally involve you being looked after in Intensive Care immediately after surgery. This allows us the opportunity to approach you beforehand to ask if you would consent to participate in this study.

Signing up to the study

After reading this information leaflet you will have the opportunity to discuss the study with a member of the research team and ask questions. If at this stage you are happy to participate, we will ask you to sign a consent form. If you would like more time to consider taking part, we will arrange a time to contact you prior to your operation to rediscuss participation.

If you agree to participate, we will ask you to sign a consent form prior to your operation.

If you decide not to take part in your study, then you continue with your planned surgery as normal.

If you agree to participate but later change your mind, then you can withdraw from the study at any time. You can do this by contacting one of the research team via telephone or email (at the end of this document), or by asking any member of the team looking after you who will be able to assist you.

Why am I being asked to participate now?

We are approaching you to participate in the study prior to your operation as the study is investigating aspects of your care (how to best look after your magnesium levels) immediately following an operation. In many cases in the immediate period following an operation you may lack the capacity to consent due to effects of the surgery, general anaesthesia and pain medications, but in the majority of cases this resolves in the first 24 hours. It is important that we study how best to give you treatments in the immediate period following surgery, so we are asking for your consent in advance.

What happens in the study?

If you agree to participate in the study, you will go ahead and have your operation as normal. After surgery you will come to the Intensive Care Unit afterwards. Occasionally, your clinical team may decide that you don't require Intensive Care, and can be safely looked after on the ward. If this happens, you'll still be able to take part in the study by undertaking an interview, although you won't be involved in the study of the computer prompts, as these are only being used in Intensive Care.

On the Intensive Care Unit, you will continue to be looked after as normal. As part of your routine care after an operation you will have regular blood tests (normally once a day for the first few days), including measurement of the amount of magnesium in your blood. How often these blood tests are conducted is decided by your clinical team and not by the study.

Once your blood test results are back, the Intensive Care nurse looking after you will receive the computer prompt as detailed above and decide how best to look after you, together with the rest of

the clinical team. The computer prompt will repeat for each new blood test result you have, for the duration of your stay on Intensive Care, or a maximum of five days after your operation.

Because the prompt displays to the nurse using the electronic patient record on the bedside computer, you may not be aware of it happening. Like all the medications that you receive, the nurse will let you know if they are giving you magnesium before giving it. You are free to discuss the computer prompt and magnesium decision with the nurse if you would like, this will not affect the study.

It is important to stress that the computer prompt will not ask the nurse to do anything outside normal clinical practice. Your nurse, together with the rest of the Intensive Care team retains control over the treatment you receive at all times.

When you are well enough to transfer from Intensive Care to the ward, the computer prompt will stop functioning. On the ward, when you are well enough, we will ask you to undertake a follow up interview, which should take approximately 30 minutes. Following this interview, your participation in the study will be finished.

How will we collect the interview data?

After confirming you remain happy to proceed, one of the research team members will conduct the interview which will be audio recorded. The digital recordings will be uploaded to a secure research environment, managed by University College London. A member of the research team will then transcribe the recordings into writing in order to analyse them, and at this point all identifying features will be removed. Following completion of the study, removal of identifiers and transcription, the audio recordings will be deleted.

Who will have access to the data?

Access to the data will be restricted to members of the study research team, detailed within the study protocol. Any information you provide during the interview will be anonymised by removal of identifying features by a member of the study team. We will use selected quotes without names or identifiers in the published study results.

What are the possible benefits of participating in the study?

This study is for research purposes and will provide no direct benefit to you. In the long-term this study will contribute to developing new clinical research methods to improve how we deliver care to critically ill patients at UCLH.

What are the potential disadvantages of participating in the study?

If you agree to participate in the study, we ask that you undertake one follow up interview after leaving Intensive Care, lasting approximately 30 minutes.

What happens if you don't participate in the study?

Your participation is entirely voluntary and you are free to decline or withdraw from the study at any time. Your participation in this study does not alter your planned surgery, or postoperative care in any way beyond that detailed here.

What happens after the study?

After completing the pilot study, we will analyse the results. We hope to use these pilot results to optimise the design if the computer prompts, and then run a large-scale trial in the future. If you would like to be kept informed about the results and progress of the project, we will happily keep you updated via email (with your consent).

What if something goes wrong?

Every care will be taken in the course of this study. However, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff during your participation in a research study, NHS or UCL complaints mechanisms are available to you. Please ask your research doctor (or a member of your clinical team) if you would like more information on this.

If you remain unhappy and wish to complain formally, you can do this using the NHS complaints procedure. Details can be obtained from the University College London Hospital Patient Advice and Liaison Service (PALS). PALS can be contacted online (https://www.uclh.nhs.uk/contact/patient-advice-and-liaison-service-pals) or by telephone (0203 447 3042), or email: uclh.pals@nhs.net.

Do you receive compensation for participating in this study?

Participation in the study is entirely voluntary and does not include any expense or payment.

Who is organising and funding this study?

This study is organised by a team of researchers and clinicians from UCL and UCLH. It has received sponsorship from UCL.

What are the ethical and legal aspects in this study?

This study has been approved by University College London Hospitals, and is being carried out in accordance with national legislations and guidelines as detailed in the amended Declaration of Helsinki (Seoul, 2008). This study has been reviewed and approved by a Research Ethics Committee.

How will we use information about you?

We will need to use information from your electronic medical record for this research project. This information will include features to identify you as a study participant, including your name, hospital identification number and date of birth. We will also use data which is normally collected as part of your clinical care, including heart rhythm observations, when and how you receive additional magnesium treatments, and additional clinical data designed to answer the study question. Your clinical data will remain inside University College London Hospital's computer systems, accessible only to designated members of the research team, and the study sponsor (UCL).

Once we have finished the study, we will keep some of your data, so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

We also need to manage your records in specific ways for the research we conduct to be reliable. This means that we won't be able to let you see or change the data we hold about you.

If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study. This data will remain securely stored in University College London Hospital IT systems and in the UCL Data Safe Haven.

Where can you find out more about how your information is used?

You can find out more about how we use your information:

- At www.hra.nhs.uk/information-about-patients/
- By asking one of our research team
- By sending an email to: matthew.wilson8@nhs.net , or: uclh.criticalcareresearch-dl@nhs.net
- By phoning us on: 07722407413
- By sending an email to data-protection@ucl.ac.uk

If you have further questions:

Contact the principal investigator (Dr. Matthew Wilson – matthew.wilson8@nhs.net), or the chief investigator (Dr. Steve Harris – steve.harris@ucl.ac.uk):

- If you have any questions concerning your participation in this research study
- If you have questions about your rights as a study participant
- If you have questions, concerns or complaints about the research

S3 – Study Consent Form

University College London Hospitals NHS
NHS Foundation Trust

IRAS ID: 279737

Centre Number: 1

Study Number: 142382

Version Number: 1.1 (05.11.21)

Participant Information Number:

CONSENT FORM

Title of Project: **PROSPECTOR-Critical Care**

Name of Researcher: Dr. Matthew Wilson

Please initial each box:

1. I confirm that I have read the information sheet dated **5th November, 2021** (version 1.1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes (patients) and data collected during the study may be looked at by individuals from the study research team, from regulatory authorities or from the NHS Trust or University College London, where it is relevant to my taking part in this research. I give permission for these individuals to access my records. ☐

4. I understand that the information held and maintained by University College London Hospitals and University College London may be used to help contact me or provide information about my health status. ☐

5. I agree to participate in the study interview program and consent to the interview being audio recorded and transcribed into writing. ☐

6. I agree to take part in the above study. ☐

Name of Participant	Date	Signature

Name of Person taking consent	Date	Signature

SPIRIT Checklist

Item	Description	Reference
1/ Title	Descriptive title identifying the design, population, interventions and acronym	P1
2/ Registration	2a/ Identifier and registry name 2b/ WHO Trial registration data set	P3 (needs completing) ? table/supp materials
3/ Protocol version	Date and version ID	Version 1.0, 22/9/21
4/ Funding	Sources and types of support	P21
5/ Roles and responsibilities	5a/ Names, affiliations and roles of contributors 5b/ Name and contact information for the trial sponsor 5c/ Role of sponsor and funders 5d/ Committees	P21 UCLH/UCL Joint Research Office. uclh.randd@nhs.net 4th Floor, West 250 Euston Road London NW1 2PG Approval and sponsorship of trial protocol. Oversight of trial conduct and data collection. Study Steering Group: Dr Matthew Wilson (PI) Dr Steve Harris (CI) Prof Folkert Asselbergs (Study Advisor) Dr David Brealey (Study Advisor) Prof Matt Sydes (Statistical Advisor) Mr Ruben Miguel (EHRS Analyst)
6/ Background and Rationale	6a/ Research question and justification, summary of existing work 6b/ Choice of comparators	P4 + Main protocol P9
7/ Objectives		P7
8/ Design	Type of trial	P8
9/ Setting	Description of study setting	P8

10/ Eligibility criteria	Incl/Excl criteria	P8
11/ Interventions	11a/ per group description 11b/ stopping criteria 11c/ adherence strategies 11d/ usual care	P9 P9 + main protocol NA P9
12/ Outcomes	Primary & secondary and data	P10-11
13/ Participant timeline	Enrolment, interventions, visits	P16, GANTT in main protocol
14/ Sample size		P11
15/ Recruitment		P8
16/ Allocation	16a/ Sequence generation 16b/ Allocation concealment 16c/ Implementation	P9 NA P9
17/ Blinding	17a/ Who 17b/ Unblinding	NA NA
18/ Data collection	18a/ Collection of outcome, baseline, trial data, data quality 18b/ List of outcome data to be collected for participants who withdraw	P10-11 + main protocol + supp. Materials for interview schedules See consent forms (use data collected up till point of withdrawal)
19/ Data management		P12 + main protocol
20/ Statistical methods	20a/ primary and secondary outcome analysis 20b/ subgroup analyses 20c/ Effect estimate method and missing data handling	P11 + main protocol NA NA
21/ Data monitoring	21a/ Data monitoring committee or explanation of why not needed 21b/ Interim analyses and stopping guidelines	See steering committee and main protocol NA
22/ Harms	Adverse event reporting	Main protocol
23/ Auditing	Frequency and procedures for auditing trial conduct	As per UCL(H) sponsorship guidance.
24/ REC approval		P3 + P12
25/ Protocol amendments	Plans for communicating protocol modifications to relevant parties	Via UCLH Joint Research Office
26/ Consent	26a/ Who will obtain consent and how	P8

	26b/ Additional provisions for participant data collection	Nil additional.
27/ Confidentiality		P12 and main protocol
28/ Declaration of interests		P21
29/ Access to data		P12 and main protocol
30/ Post trial care		Sponsorship and insurance, contact details on Participant information sheets
31/ Dissemination policy	31a/ Communication of results 31b/ Authorship eligibility guidelines and professional writers 31c/ Plans for granting public access to full protocol, participant level dataset and statistical code	P12 NA NA
32/ Informed consent materials	Consent form and PIS	Available on request
33/ Biological specimens		NA