Programme plan

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{>>Target 5000 words<<}

# Title

REMAP-nudge: leveraging the Critical Care Health Informatics Collaborative to build a learning health care system for peri-operative medicine

# Aim and objective (aka hypothesis)

When there is genuine equipoise between two commonly used treatments, *not* doing a point of care trial to find out which has a better risk/benefit profile seems *unethical*. Pragmatic RCTs could enable clinically important questions that can be answered fast based on studies carried out in routine care settings on a full range of participants.

**Learning Health Care Systems in the NHS**. Nuffield Trust Seminar, January 2019(*1*)

## Hypothesis

That there is a portion of clinical care that can be optimised in a methodologically rigorous and ethically sound manner without resorting to standard parallel arm randomised controlled clinical trials.

## Aim

This project aims to develop the framework for a learning health care system for peri-operative medicine using established infrastructure at a single site but with a proven ability to scale to multiple sites.

### Deliverables (Work packages)

1. A high-quality prospective peri-operative medicine database built to scale across multiple NHS sites
2. A pair of exemplar physician-prescribing preference studies
   1. Comparison of conservative versus liberal oxygen targets on post-operative morbidity following high risk surgery admitted to critical care
   2. Comparison of high versus low targets of Magnesium supplementation on post-operative atrial fibrillation following high risk surgery admitted to critical care
3. A programme of work leading to a pilot embedded randomised controlled trial using a novel *nudge* design also built to scale across multiple NHS sites (**REMAP-Nudge**)

I provide two worked examples (2a and 2b). However, this proposal is methodological, and other clinical questions would also be suitable, and may be prioritised by the integrated patient and public involvement (PPI) pathway.

# Background

**Learning health care systems** "… integrate the practice of medicine and the generation of reliable medical evidence in a way that will promote both continuous learning and evidence based medical practice.(*2*) This programme of work integrates digital health and *nudged* rather than *mandated* randomised interventions to create a safe, ethical delivery framework for this oft-cited and yet rarely implemented goal. I specifically focus on optimising the delivery of routine health care where pre-existing variation in practice implies clinical equipoise. The end result would be a system that delivers causally robust personalised treatment effects at scale.

I build on the following three concepts: digital health, nudged interventions, and variation in practice:

1. **Digital health**

Digital health can potentially offer the solutions needed to transform clinical trials … However, this cannot be accomplished by replicating the current research processes and just transforming them from paper to digital form … Rather, a complete re-thinking and re-engineering of the clinical trial experience around the participant rather than the research site is needed.(*3*)

1. **Nudged interventions**

A nudge … is any aspect of the choice architecture that alters people’s behavior in a predictable way without forbidding any options … Nudges are not mandates.(*4*)

1. **Variation in practice implies clinical equipoise and treatment heterogeneity**

* equipoise[[1]](#footnote-1): … honest, professional disagreement among expert clinicians about the relative clinical merits of interventions A and B for a particular patient population(*2*)
* treatment homogeneity versus heterogeneity(*5*):
  + homogeneity: treatment B is superior to treatment A for (almost) everybody in the designated population;
  + heterogeneity: treatment B is superior to treatment A for an average or typical subject in the designated population. *B may be inferior for a non-trivial proportion of subjects*.

Most importantly, it is crucial that this proposal is not read as a criticism of randomised controlled trials (RCT) in general. Rather this is an adaption of the RCT methodology to meet the need to deliver evidence based personalised medicine recommendations. As such, this approach is inappropriate for the investigation of novel drugs and interventions (e.g. CTIMPS, ATIMPS and other scenarios).

## Narrative

**Hundreds of millions of decisions** are made every day by doctors, nurses and allied health professionals. Most decisions are so small and routine that we don’t always notice them: do we give paracetamol for a fever? do we target an oxygen saturation of 94% or 98%; do we stop the antibiotics this morning or this afternoon? But it is inconveivable that the aggregate effect of all these decisions is not important.  
Randomised controlled trials (RCTs) are our ‘go to’ method for studying a single decision. But **traditional RCTs are slow, expensive and cumbersome**. Moreover they deliver results that are true on *average* but not adapted for the individual. Personalised medicine recognises that variations in genotype and phenotype require treatments to be appropriately adapted. With unlimited sample size, such evidence could be generated but the cost would be prohibitive. Machine learning (ML) offers to use ‘big data’ to derive endotypes[[2]](#footnote-2) but without randomisation observational research remains vulnerable to bias through unmeasured confounding. This is also true for Artificial Intelligence (AI) techniques such as reinforcement learning.(*6*, *7*)  
Parallel two arm (A vs B) RCTs are now being replaced with intelligent designs such as REMAP (**Randomised Embedded Multifactorial Adaptive Platform**) trials.(*8*) This automates data collection by **E**mbedding the trial in electronic health record (EHR). It **A**dapts the randomisation algorithm so that as a signal for benefit or harm emerges patients are preferentially allocated to the best strategy. And finally, **M**ultiple treatments (factors) are evaluated together using the same **P**latform so the cost of setting the trial up is shared. REMAP-CAP is the first attempt at this approach evaluating antibiotics, anti-virals and steroids for Community Acquired Pneumonia (CAP).(*9*) Nonetheless, this is still a hugely expensive international collaboration recruiting initally 2800 patients across 50 sites over several years.(*10*)  
The final result from REMAP-CAP will true *on average* but cannot provide the right answer for the each patient who may have an allergy to the ‘best’ antibiotic, or be more susceptible to the immune suppression induced by the steroids, and so on. This **treatment heterogeneity** is driven by subtle endotypes not exposed by the RCT.(*11*) And herein lies the skill of the clinician. To take that average answer and decide if it applies to the particular situation. But while there is shared expertise, each clinician’s personal experience creates variation.  
We normally see such variation as a problem.(*12*) Electronic Health Record Systems (EHRS) often provide clinical decision support tools to improve compliance with evidence and reduce variation. It is assumed that the busy clinician who is more often unwittingly deviating from a guideline rather than personalising treatment.  
But what if we used decision support to both **reduce variation where strong evidence is available, *and* to learn from the existing variation where evidence is sparse**.  
We call this approach ***nudge learning***, and propose a methodology called ***REMAP-Nudge***. This design will ultimately depend on *presumed* (opt-out) consent to allow the trial to scale, and through scale investigate treatment heterogeneity. However, such a paradigm shift in clinical trial implementation requires a pragmatic and stepped approach. This project proposes a stepped implementation building first (1) a high quality database to confirm treatment variation and capture the rich data needed for an embedded RCT; then (2) a programme of work that carefully evaluates patient and clinician acceptance of a nudge methodology; and (3) implements a pilot REMAP-Nudge trial in high risk surgery to estimate nudge compliance, and likely treatment effect sizes. The design is such that if successful the pilot study will then transform to a multi-site learning health care programme to optimise care of the high risk surgical patient.  
We argue that this is the perfect domain in which to develop this methodology because **we leverage the anaesthetic pre-assessment clinic** to run the initial work using a *pre-emptive* rather than presumed consent model.

# Project plan

This 4 year programme will build on two existing programmes. Firstly, the established **Critical Care Health Informatics Collaborative** (CCHIC) programme that holds data on 45000+ adminssions from 10+ NHS ICUs.(*13*) The existing governance and data flows create an opportunity to magnify the influence of the RCOA/BOC grant to scale across multiple sites. Secondly, the **Experimental Medicine Application Platform** (EMAP) at UCLH where we have a proven track record of deploying novel applications in realtime against the hospital wide EHRS. More specifically, my team has spent the last two years building EMAP exactly to enable this sort of work.  
EHR systems alone do not permit innovation and development. They are hampered by vendor lock-in, and by the need to prioritise clinical safety and reliability above all else. EMAP is a data science platform built for the NHS inside the NHS according to the following principles (1) Protection of operational systems by deploying a live mirror of the EHRS (2) Protection of patient privacy by following a ‘code-to-data’ rather than ‘data-to-code’ paradigm (3) Health care interoperability to permit cross-site collaboration and (4) Open source to foster a community of practice.

## Work package 1: CCHIC-Peri-op

**Objective: Build an extension to the Critical Care Health Informatics Collaborative (CCHIC)**

The NIHR established the Health Informatics Collaborative in 2014. UCL/UCLH has led the Critical Care theme.(*13*) I have co-led the project (with Singer/Brealey/MacCallum) since 2015. We have ethics (REC 14/LO/103) and CAG approval (14/CAG/1001) plus data sharing agreements for 7 UK sites (including Cambridge/GSTT-Kings/Imperial/Oxford/UCL and now the Royal Marsden and Bristol). Routinely collected clinical data from critical care admissions is transferred to UCL’s ISO/IEC 27001:2013 compliant [data safe haven](https://www.ucl.ac.uk/isd/services/file-storage-sharing/data-safe-haven-dsh) where it is organised, cleaned, linked to Hospital Episode Statistics ([HES](https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics)) to define health care utilisation and long term survival, and then made available as resource back to the critical care community.  
Since 2015, **we have curated data for >45,000 admissions to critical care with 250 data items and >250 million data points**. This resource has led to a series of publications(*14*, *15*), and high profile presentations (Hot Topics, Intensive Care Society 2019). We have also launched an educational programme including datathons and training courses for clincal data scientists.(*16*) We have had a favourable review of our ethics (2019 5 year review), and ongoing support at PPI events.

* we will extend the scope of the ethics and the collaboration agreements with participating sites to the same cohort studied under the recent 2nd Sprint National Anaesthesia Project (SNAP-2 EpiCCS: Epidemiology of Critical Care after Surgery).(*17*) That is **patients staying in hospital overnight undergoing a surgical or interventional procedure that requires the prescence of an anaesthetist**.
* we will expand the data specification to include **key case mix measures for peri-operative medicine** (patient comorbidites, risk factors, surgical procedures, anaesthetic techniques and intra- and post-operative complications) leveraging experience with SNAP-2, PQIP(*18*) and NELA(*19*)
* we will standardise and generate **five high quality outcome measures** from these data (1) mortality (2) length of stay (3) planned and unplanned critical care admission and (4) POMS(*20*) and (5) using the existing CCHIC permissions (HES/ONS) to define health care utilisation and long term survival
* we will add metadata to all drugs, orders, and treatment decisions to capture a pseudonymised identifier for the clinical decision maker to build evidence for variation in practice, and preparatory physician-prescribing preference studies(*21*)
* the scale and scope of data collection requires hospitals that have integrated Electronic Health Records (EHRs). The interventional arm of the study further requires a working clinical decision support technology. We have already had a favourable response from approaching the Cambridge BRC (see attached letter of support from Dr Ari Ercole).

We would see this CCHIC:Peri-op becoming the *premier international resource for observational studies of high risk surgery and peri-operative medicine*. Just at UCLH trust (including RNTNE, NHNN, WMS) we would expect to recruit >10,000 patients per year. Using the NIHR Health Informatics Collaborative network as a springboard alongside extensive and broad networks developed running SNAP-2/EpiCCS, we would seek funding to expand to further sites during the 4 years.

## Work package 2: REMAP-nudge design

**Objective: (1) Generate evidence of variation in practice using Physician Prescribing Preference studies and (2) Run a feasibilty study to test the REMAP-Nudge design**

We have prepared two worked examples but it should be noted that in the actual project, the interventions to be tested will be developed and selected via a joint clinician/patient/public programme, and not investigator driven. This is especially important given that we will be moving to a presumed consent model, and that we will depend on the clinical workforce to engage with the **nudge** approach. Hence the actual questions to be studied may vary. Further examples might include

* Titration of noradrenaline to target mean arterial blood pressure
* Titration of inspired oxygen to target haemoglobin saturation
* Transfusion of packed red cells to target haemoglobin concentrations
* Supplementation of magnesium and potassium based on plasma concentrations
* Fluid balance targeting after elective surgery
* Duration of routine antibiotic therapy following elective surgery

The intervention that is chose will then be worked into a study protocol and submitted for approval by NHS Research Ethics. The purpose of the study is to prove that the nudge-randomisation tool is technically feasible to implement, and that we can deliver an effective PPI framework that will monitor its acceptability.

### Physician Prescribing Preference (PPP) studies

These studies exploit natural variation in practice. A classic example comes from the psychiatric literature where GPs have been show to have consistent preferences for different classes of Selective Serotonin Uptake Inhibitors (SSRIs) and Tricyclic Antidepressants (TCAs).(*22*) Patients treatments therefore depended on which GP they attended. Given that GP assignment can be argued to be unrelated to the self-harm/suicide (after controlling for social deprivation etc.) then this permits an evaluation of the relative effectiveness of these drugs. Comparable examples in critial care and peri-operative medicine would include transfusion triggers, oxygen targets, blood pressure targets, and antibiotic duration etc.

We will use the pseudonymised reference to the prescriber capture in CCHIC-periop to define physicians prescribing preference as intercept estimates from a multi-level model (e.g. the administration of Magnesium would be the dependent variable with serum Magnesium and previous AF as the independent variables, and the prescriber as a random effect).

Because prescribing preference is only on of many factors that affects the treatment decision then there is imperfect compliance. In other words, we are imagingin an RCT where the patient’s exposure to a pro- or anti- Magnesium ‘top-up’ clinician is the random coin toss. Other factors may trump the prescriber’s preference (i.e. recent arrhythmias) but where the prescriber is otherwise indifferent then their inherent preference will affect the decision. For these marginal cases, we can use an Instrumental Variable (IV) technique to evaluate the causal effect of Magnesium on subsequent arrhythmias.

This method therefore both demonstrate the degree of exising variation in practice, and gives us an initial look at the likely effect size. We would repeat these studies as part of the evaluation pathway for any intervention being considered for REMAP-nudge.

## Feasibility study

### Experimental design and methods

### Design

Prospective randomised feasibility study.

### Study Population

###### Inclusion Criteria

Elective oeseophagectomy patients undergoing surgery in a single tertiary referral centre. 3 month convenience sample.

###### Exclusion Criteria

Non-admission to critical care postoperatively.

### Study Centre

University College London Hospital, Euston Road, London.

35 bedded mixed medical and surgical ITU. ICU admission is determined by consultant in charge but it is accepted practice that all patients undergoing elective oeseophagectomy are admitted to ICU for 4 to 7 postoperative days.

Patient admissions are conducted by a mixed junior doctor cohort (Core Trainee 1 to Specialist Trainee 7) including medical, intensive care and anaesthetic trainees. Admission documentation is via an electronic patient record proforma.

### Data Collection Framework

Existing routinely collected clinical data from multiple electronic record systems on the ICU. The EHRS contains a pre-existing framework for integrating research, including a randomisation module to enable randomisation at the level of the individual patient record. Having demonstrated patient and clinician acceptability of this tool, future work will embed this within the EHRS.

All data collection, storage and analysis will occur within the UCLH IT system framework using the EMAP platform.

### Recruitment

Patients will be recruited from Anaesthetic Pre-assessment Clinic prior to surgery, by the local research registrar. At this point decision to undergo surgery will have been taken. Patients will receive a study information sheet and an explanation of the study from the recruiter. Following this they will be offered an opportunity to provide written consent to the study.

### Patient Journey/Study Flow

A close up of a map

Description automatically generated

Following recruitment, patients will undergo a semi-structured interview conducted by the local research. This will detail their knowledge, thoughts and ideas surrounding the concepts of variation in practice, the acceptability of pre-emptive and opt-out consent models and nudge randomisation.

Patients will subsequently present for surgery, undergo their operation and be admitted to the critical care unit postoperatively. The study coordinator will be alerted to the patient attending for surgery by a prespecified alert on the EHRS or by email communication with the surgical team.

If surgery is cancelled then the patient will remain within the study as long as the relisted procedure date occurs within the data collection time period. If the patient is not admitted to critical care postoperatively they will be excluded. The first 24 hour period will be taken from postoperative day one (i.e. the day after surgery).

On postoperative day one, the critical care physician looking after the patient will be approached by the research registrar prior to conducting the patient’s daily assessment.

They will be informed that the patient has consented to the study and be presented with the study proforma and a numbered, sealed randomisation envelope.

Following conduct of the daily assessment, the physician will be prompted to prescribe a Magnesium target target for the day. Following recording of the target, the sealed envelope will be opened and the physician will view the study nudge randomly selected.

This nudge will consist of:

- **An introductory descriptive line e.g**.

"Your patient is enrolled in a research study examining variations in clinician practice for Magnesium target target prescribing."

- **Allocation to a randomly selected study group e.g.**

"As part of the study we would like you to alter your previously prescribed Magnesium target target to a (high/low) threshold

- **Invitation to accept or decline the nudge**

The clinician will then go about prescribing the final Magnesium target target on the EHRS. This final Magnesium target target will be recorded and compared with the nudge grouping to gauge overall compliance with the nudge.

Throughout the study clinicians will retain the ability to alter the Magnesium target, either by disregarding the nudge or by subsequent alteration at any time. They will be encouraged to record any alterations to Magnesium target throughout the day using the EHRS as normal.

Following reviewing the nudge and choosing to accept or decline the clinician will undergo a semi-structured interviewfocused on the acceptability of the nudge randomisation process and their opinions regarding the proposed change in consent model.

The process is repeated on thereafter for the next 2 days of the ICU admission. The clinician will review the patient and make a Magnesium target prescription. The research registrar will then present the clinician with the same nudge and the clinician makes a second decision. This is to assess whether the potential for “gaming” of the system on day 2, particularly if the assessing clinician is unchanged e.g. “the Magnesium target was high/low yesterday so today I will make my target prescription anticipating the same modification today”. If there is a new clinician on postoperative day 2, a second semi-structured interview will be conducted.

Data collection ceases after completion of 48 hours of postoperative critical care admission.

If a patient is transferred to the ward or dies before this time they will be excluded.

Following hospital discharge patients will be followed up in surgical outpatient clinic. At this juncture they will undergo a second semi-structured interview focusing to assess if their views on the process have changed.

### Sample Size

This feasibility study will provide data on recruitment rates to inform sample size calculations for future similar work.

The study centre sees approximately two elective oesophagectomy patients per week. Assuming a recruitment rate of 50%, across the study period we would expect a sample size of 10 to 15 patients.

This sample size will be insufficient to power any clinically relevant outcomes, however will demonstrate the feasibility objectives of the study, whilst gathering rich qualitative information regarding changes to consent models and nudge randomisation. Compliance with the nudge will help evaluate future sample size calculations.

# Statistical Considerations

Due to the nudge being suggested rather than mandated there will inevitably be an imperfect accrual rate to all groups and uneven sample sizes between all groups. We will therefore use a statistical technique called instrumental variable analysis (IV) that permits causal inference when compliance with randomisation is imperfect for a portion of the population.

# Expected Outcomes

## Primary Outcome:

Clinician compliance with "nudge".

Number of times in the intervention arm that the clinician agrees to the "nudge", compared with the total number of opportunities to comply i.e. "nudge" efficacy. Including variance of nudge compliance across treatment groups.

## Secondary Outcomes:

1. Qualitative semi-structured interview data from patients and families:
   1. Existing knowledge of variation in practice as a concept.
   2. The acceptability of a pre-emptive consent model.
   3. The acceptability of clinician "nudge" randomisation tool.
2. Qualitative semi-structured interview data from clinicians:
   1. Existing knowledge of variation in practice as a concept.
   2. The acceptability of a pre-emptive consent model.
   3. The acceptability of clinician "nudge" randomisation tool.
3. Variation in Magnesium targets
4. Actual Magnesium delivery.
5. Prevalence of atrial fibrillation or other arrhythmias

# Safety Considerations

## Intervention

One of the attractive aspects of this methodology is that throughout the process the clinician retains overall control over the application of the "nudge". Secondly, we ensure that the magnitude of the nudged target is always within routine clinical variation, and well within the variation seen in the PPP observational studies. Finally, the study will be conducted within a critical care unit where patient physiology is continuously monitored, and adjustment to targets continuously possible.

## Data Safety

All patient identifiable data and study data will remain stored on NHS EHRS systems, behind the EHRS firewall. Data analysis will also be conducted within this environment.

## Trial Conduct

A data safety monitoring committee will oversee the running of this trial. It is anticipated they will meet prior to implementation to review study protocol and thereafter monthly during data collection.

## Work package 3: REMAP-nudge pilot

**Objective: Pilot the REMAP-nudge design using pre-emptive rather than presumed consent; estimate nudge compliance, recruitment, and effect size; prepare for a major programme grant**

Work package 3 is summarized in brief because of space constraints. In essence, the same design as outlined above will be implemented but with the aim of estimating nudge compliance and effect size in a full population. We would use the existing clinical trials research infrastructure and research nurse team (with an application to the CRN) to recruit at scale in the pre-assessment clinic. Ideally, we will implement more than one study question.

There will be an initial period of safety evaluation of the nudge-randomisation software in order to gain MHRA compliance. Once this is approved, we would recruit *all* high risk surgical patients being admitted for an overnight stay to critical care (estimated 1,500+ admissions per year at UCLH and Westmoreland Street Hospitals).

Within 3-6 months, we would have developed sufficient pilot data to prepare an application for a major programme grant. Given the explicit interoperability in the software design, we would be able to scale these to other sites with integrated EHR systems. The same data monitoring committee would help guide through both the adaptive randomization process, and safety monitoring the decision to continue or retire each intervention from the study.

# Endnotes

# References

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1. This is a more practical statement of theoretical equipoise which may be defined as “a state of uncertainty in the mind of the individual investigator regarding the relative merits of interventions A and B for some population of patients. When investigators are in such a state of uncertainty they do not knowingly disadvantage patients if they allow treatments to be allocated by a process that supports reliable medical inference, such as randomisation.” [↑](#footnote-ref-1)
2. endotypes refer to distinct pathophysiological mechanisms within a disease entity that respond differently to treatments (i.e. create treatment heterogeneity) and therefore justify the idea of ‘personalised medicine’ [↑](#footnote-ref-2)