SPRINT NATIONAL ANAESTHESIA PROJECT 3: AN OBSERVATIONAL STUDY OF FRAILTY, MULTIMORBIDITY AND DELIRIUM IN OLDER PEOPLE IN THE PERIOPERATIVE PERIOD

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SYNOPSIS

Title	SNAP3: AN OBSERVATIONAL STUDY OF FRAILTY, MULTIMORBIDITY AND DELIRIUM IN OLDER PEOPLE IN THE PERIOPERATIVE PERIOD
Acronym	SNAP 3
Short title	SNAP3: Frailty & Delirium
Chief Investigator	Iain Moppett
Objectives	To characterise the epidemiology of frailty, multi-morbidity and postoperative delirium in approximately 12,000 older people undergoing surgery in the UK a) Examine the relationship between frailty, multimorbidity and perioperative outcomes across all surgery types b) Describe the variation in hospital-level and patient-level frailty-related interventions c) Identify associations between hospital-level and patient-level frailty-related interventions and outcome d) Develop and internally validate a risk-prediction tool for postoperative delirium
Study Configuration	Prospective, multi-centre, observational cohort study
Setting	Secondary care
Sample size estimate	We calculated sample size requirements for all planned analyses. The maximum of the required sample sizes is around 11,000, under very cautious assumptions.
Number of participants	Estimated as around 12,000
Eligibility criteria	People aged 60 years or older undergoing any surgery in NHS hospitals during up to two periods of up to seven days • Day-case, emergency, and elective surgery • General, neuraxial and regional anaesthesia
Description of interventions	Data will be collected from five sources: 1. Medical notes review (demographics, medical history, type of surgery, ASA) 2. Laboratory results 3. Direct patient report and observation (frailty tool, post-operative morbidity survey (POMS), delirium assessment, Quality of Life (QoL) scores) 4. Linkage with other data sets e.g., HES 5. Report of workload and activities from on call teams

Duration of study	Planned start date: October 2021 18 months for the study Direct participant involvement: up to 7 days at initial admission; telephone follow-up at 120 days
Methods of analysis	Analyses of the relationship between frailty, multimorbidity and outcomes will employ multilevel models, using binomial error distributions with logit link for binary outcomes, and multilevel quantile regression for numeric outcomes. Multiple imputation of missing covariate values will be considered in the context of data quality and likely processes of missingness. The risk model for post-operative delirium will be developed following procedures recommended in the statistical literature, including penalized regression and optimism correction via bootstrapping.

ABBREVIATIONS

CAM-ICU	Confusion Assessment Method-Intensive Care Unit
CFS	Clinical Frailty Scale
CI	Chief Investigator overall
CIS	Consultee Information Sheet
CoLI	Co-Lead Investigator
CRF	Case Report Form
DAOH	Days alive and out of hospital
DAH	Days at home
EQ-5D-5L	Euroqol 5 Dimensions 5-levels quality of life assessment
GA	General Anaesthesia
GCP	Good Clinical Practice
HSRC	Health Services Research Centre
ICU	Intensive Care Unit
IMD	Index of Multiple Deprivation (IMD)
IDAOPI	Income Deprivation Affecting Older People Index
NHS	National Health Service
PCPIE	Patient, Carer and Public Involvement and Engagement Committee at the Royal College of Anaesthetists
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
PLR	Personal Legal Representative
POMS	Postoperative morbidity survey
PPI/E	Patient and Public Involvement/Engagement
RCoA	Royal College of Anaesthetists
REC	Research Ethics Committee
R&D	Research and Development department
SMG	Study Management Group

SNAP	Sprint National Anaesthesia Project
SORT	Surgical Outcome Risk Tool
TIVA	Total Intravenous Anaesthesia
UoN	University of Nottingham

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STUDY BACKGROUND INFORMATION AND RATIONALE

The number of older people undergoing surgery globally is increasing due to demographic changes and improvements in surgical and perioperative care.

Frailty is an age-related syndrome that increases an individual's vulnerability to adverse outcomes in response to stressors such as illness, injury and surgery. There is reasonable evidence that surgical outcomes are worse in the presence of frailty. The largest study of frailty and surgical outcomes using administrative data and a binary frail/non-frail categorisation for elective major non-cardiac surgery found that the impact of frailty was dependent on surgery type, age (the independent impact of frailty is less as age increases)) and greatest in the early perioperative period. Whilst the link between socioeconomic status, frailty and health outcomes is well-described in the community setting, less is known about these factors in the surgical setting. Furthermore, little is known about the importance of particular domains of frailty and the relationship with surgical outcome.

Screening for frailty is increasingly advocated but there is a lack of consensus on which tool to use for screening and/or diagnosis in the perioperative setting. Recent systematic reviews have highlighted the heterogeneity of frailty measurement tools which may be one contributor to a lack of standardised approach to modifying the frailty syndrome in the perioperative setting with the aim of improving surgical outcomes. This is further complicated by the acknowledged limitation of many 'frailty' tools which are instead counts of multimorbidity as opposed to multidomain assessment tools. Distinguishing between multimorbidity and frailty is important given the recognition that seven out of ten frail individuals also display multimorbidity, but only two of ten patients with multimorbidity are also frail.

Delirium is a distinct clinical syndrome associated with adverse outcomes following surgery. Less is known about the influence of severity, timing or form (hyperactive or hypoactive) of delirium on postoperative outcomes. To date, there is no effective pharmacological treatment to prevent delirium, with evidence instead supporting non-pharmacological multicomponent interventions aiming to reduce the incidence of delirium through targeting the triggers for the syndrome, in addition to reducing severity.

Whilst evidence supports commonality in the aetiology and pathogenesis of frailty and delirium, less is known about the interface of these distinct syndromes in the perioperative setting. The initial suggestion from the data is that these two conditions confer cumulative negative effect on postoperative outcomes, but this requires further exploration at scale.

A key question for researchers, clinicians, those responsible for planning perioperative services, and most importantly, patients and their families, is therefore, how to identify frailty and risk of delirium in routine clinical settings, what to do with frailty, multimorbidity and delirium risk in the time before surgery and how these conditions should be managed during and after surgery. This study will generate a large, high-quality dataset on a cohort of older people undergoing a range of surgical procedures to help address these questions.

Although there may be epidemiological merit in understanding the prevalence and associated outcomes, this information only really has value if:

a) it adds more than we currently know
b) it changes how we provide perioperative care, either currently or in the future
c) it enhances the quality of information provided to patients as they make choices regarding treatment options

It is not possible for this study to answer every question about surgery, frailty, multimorbidity and delirium. This study's main focus is on the impact and management of frailty but will attempt to answer key questions about postoperative delirium.

STUDY OBJECTIVES AND PURPOSE

PURPOSE

To describe the impact of frailty, multimorbidity and delirium, and their management, on outcomes following surgery

PRIMARY OBJECTIVE

To characterise the epidemiology of frailty, multi-morbidity and postoperative delirium in approximately 12,000 older people undergoing surgery in the UK

SECONDARY OBJECTIVES

- Examine the relationship between frailty and perioperative outcomes separately by surgery types
- Examine the relationship between multimorbidity and perioperative outcomes separately by surgery types
- Examine the relationship between frailty and multimorbidity in the older person undergoing surgery
- Describe the variation in hospital-level and patient-level frailty-related interventions
- Identify associations between hospital-level and patient-level frailty-related interventions and outcome
- Develop and internally validate a risk-prediction tool for postoperative delirium

STUDY DESIGN

STUDY CONFIGURATION

Multi-centre prospective observational cohort study.

The project will involve three parallel studies:

S 1. Prospective, observational cohort study
S 2. Organisational survey of current pathways of pre- and postoperative care
S 3. Survey of referrals and interventions to general medical and geriatric medicine teams

Studies S2 and S3 are listed for reference only as they are service evaluations and will be conducted independently of this protocol.

Data will be collected from a variety of sources:

- Direct patient report and observation
- Routinely collected hospital data
- Reported (anonymised) activity from general medical and geriatric medicine teams

STUDY MANAGEMENT

The Chief Investigator has overall responsibility for the study and shall oversee all study management.

The data custodian will be the Chief Investigator.

The project will be co-ordinated by the Health Services Research Centre (HSRC) of the Royal College of Anaesthetists (RCoA).

Study Steering Committee

This will have a chair independent of the applicant, the College and Sponsor.

Members will include:

- Chair- Dr Celia Gregson, Professor of Clinical Epidemiology, Honorary Consultant Orthogeriatrician
- Chief Investigator- Professor Iain Moppett
- Trainee lead- Dr Claire Swarbrick
- PPI/E representatives – awaited
- Nursing representative – Professor Julie Sanders, Director of Clinical Research, Professor Cardiovascular Nursing
- Surgical representative –Miss Lyndsay Pearce, Consultant Colorectal and General Surgeon, Honorary Senior Lecturer
- Geriatrician representative – Professor Ruth Hubbard, Masonic Chair of Geriatric Medicine
- Primary care representative- Professor Steve Iliffe, Professor of Primary Care
- Neuroscience representative- Professor Lis Evered, Visiting Associate Professor of Neuroscience Research in Anesthesiology
- Anaesthetist representative- Dr Danny Wong, Locum Consultant in Anaesthetics
- Members of RCoA Research Team- Mr Jose Lourtie, Mrs Christine Taylor

Study Management Group

Study Management Group (SMG) members will include:

- Chief Investigator – Chair, Professor Iain Moppett
- Co-lead Investigator- Dr Partridge
- Co-investigators- Dr Akshay Shah, Dr Tom Poulton
- Trainee lead- Dr Claire Swarbrick
- PPI/E representative- Mrs Carol Green and Mr Bob Evans
- RCoA Research Team- Mr Jose Lourtie, Mrs Christine Taylor

Administrative support will be provided by the Research Team of the RCoA.

The trainee lead investigator will be undertaking a higher degree registered at the University of Nottingham. They will be responsible for day-to-day running of the study, co-ordinating with sites and local leads, analysis of data (supported by the trial statistician and the senior investigators), ensuring PPI is embedded in the study, and disseminating results.

Statistical support will be provided by a statistician employed by the HSRC.

SMG meetings will be at least monthly, and minutes taken. Progress will be reported on a minimum of a six-monthly basis to the HSRC executive management board.

Protocols, study documents and progress reports will be publicly available through a dedicated SNAP3 webpage hosted by HSRC / RCoA.

DURATION OF THE STUDY AND PARTICIPANT INVOLVEMENT

Study duration for participant involvement: 4 months (from first to final patient contact)
Study duration for data linkage: 10 years

Prospective, observational cohort study:

Study will recruit participants during up to up to two, seven-day periods.

Participant Duration:

- Follow-up on days one, three and seven (if still in hospital)
- Electronic email survey/telephone call for Quality of Life survey (EQ-5D-5L, EQ-VAS) and Days at Home estimate at four months after surgery
- Data linkage with central dataset (Hospital Episode Statistics, HES; Office for National Statistics, ONS) at four months and one, two, five and ten years.

Final follow up will be at ten years, mortality data will be linked to ONS data via NHS Digital.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

S1

The research study will take place in acute secondary care hospitals in all four nations of the UK. It is anticipated that recruitment will take place during up to two periods, of up to seven days. Estimated recruitment rates have been calculated using operational data from before the Covid-19 pandemic. As there is uncertainty about future waves of infection and reduced theatre operating, the actual number of patients undergoing operations may be less. If this study is not able to recruit it's targeted 12,000 participants initially, then a further round of recruitment may be necessary. If this were to be required, then this would be within a fortnight of the first round.

Participants will be recruited from wards and surgical admission areas. The initial approach will be from a member of the patient's usual care team (which may include the investigator). Information about the study will be on display as posters in the relevant clinical areas.

The investigator or their nominee, e.g., from the research team or a member of the participant's usual care team, will inform the participant or their nominated representative (other individual or other body with appropriate jurisdiction), of all aspects pertaining to participation in the study.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the study, the participant information sheets, and consent forms. The consent forms and information sheets will be not be available printed in other languages.

It will be explained to the potential participant that entry into the study is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time, but attempts will be made to avoid this occurrence. In the event of their withdrawal, it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

S2: Organisational Survey of Perioperative Care
The organisational survey of perioperative care will be sent electronically to the Principal Investigator from each participating site. The Principal Investigator may complete the survey personally or may delegate to another individual, for example the local Perioperative Medicine Leads. Survey reminders will be emailed to attempt to maximise responses.

S3: Survey of referrals and interventions to general medical and geriatric medicine teams
The survey of acute medical referrals will recruit those medical registrars who are on call for general medicine or geriatric medicine during the week of data collection for S1. Any medical registrar who accepts referrals or requests for advice 'in hours' and 'out of hours' will be approached.

Eligibility criteria

Inclusion criteria

People aged 60 or older undergoing any surgery during the recruitment period

- Planned day-case, emergency, and elective surgery
- General, neuraxial and regional anaesthesia
- Those with the capacity to consent or have an appropriate consultee/Personal Legal Representative available to agree participation on their behalf
- Those who return to theatre during the data collection period (will be clearly documented with SNAP3 ID -a, -b, -c suffix)

Planned day-case surgery: patients admitted for surgery with the expectation of same-day discharge (unplanned admission would be included within the day-case cohort)
Emergency: using the same definitions as used by HES
Elective: Planned / booked admissions for in-patient surgery

Exclusion criteria

- Cataract surgery
- Endoscopy performed without general anaesthesia
- Superficial surgery or minimally invasive procedures performed solely under topical / infiltration local anaesthesia (awake craniotomy for instance would be included) Details in APPENDIX 1
- ASA VI

Participants unable to consent for themselves will be eligible for the study. Details are provided in the CONSENT section.

Expected duration of participant participation

Study participants will be participating in the study for four months.

Participant Withdrawal

Participants may be withdrawn from the study either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

Informed consent

All patient participants will provide written informed consent. The informed consent form will be signed and dated by the participant before they enter the study. The Investigator will explain the details of the study and provide a participant information sheet (PIS), ensuring that the participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation. Due to the perceived low burden and risk of participation in the study and based on PPI and previous research projects undertaken by the research team in this area, potential participants will be approached and recruited in an initial meeting where they agree to this (i.e. there will not be a required cooling off period prior to recruitment).

PPI involvement has suggested that participants should be offered a full or shortened version of the PIS to improve accessibility and understanding of the PIS across our potential population.

Informed consent will be collected from each patient participant before they undergo any interventions (frailty, delirium or postoperative morbidity assessments) related to the study. It is anticipated that a hybrid approach to consent is adopted, where sites can opt to use electronic or paper consent forms. If paper consent forms are used then one copy of this will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the patient's hospital records. Electronic consent will require a tick box for each consent declaration and an electronically generated signature in line with current HRA guidance. Electronic consent forms will be emailed, printed or uploaded as required for participant, investigator and hospital records. The electronic data collection system, REDCap will hold records of the consent form centrally.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the study, continuing consent will be obtained using an amended consent form which will be signed by the participant.

For patient participants without capacity to consent

Capacity to consent to study participation will be assessed. It is essential to include participants without capacity, in order to minimise the bias of unnecessary exclusion. This study is connected with patients who have cognitive impairment. The research will not be as effective if it were to be confined to participants with capacity. This study is of low participant burden and will provide knowledge of how to manage patients similar to those without capacity. The hybrid approach for consent will be adopted as for those participants with capacity to consent. The advice or consent form will be recorded on paper or via REDCap. Copies will be offered to the participant's representative and documented in the Investigator and patient's hospital records.

England and Wales

Patients lacking capacity to consent will be handled according to sections 30-34 of the Mental Capacity Act (2005). This includes involving personal or professional consultees for those without capacity to consent. Written or telephone advice will be obtained from consultees.

Northern Ireland

Patients lacking capacity will be handled according to section 135-137 of the Mental Capacity Act (Northern Ireland 2016). This involves the use of a nominated person acting as personal

or professional consultee for those without capacity to consent. Written or telephone advice will be obtained from consultees.

Scotland
Patients with incapacity will be handled according to section 50-51 of the Adults with Incapacity (Scotland) Act 2000. This involves use of a Personal Legal Representative (PLR) for those with incapacity to consent. Written or telephone consent will be obtained from the PLR.

For patient participants who lose capacity to consent
We anticipate that a proportion of participants will lose the capacity to consent during the study. This may be due to delirium; it is necessary to continue including these participants to fulfil our research objectives.

England and Wales
Those who lose capacity to consent will be treated in accordance with section 34 of the Mental Capacity Act (2005). Information gathered about the participant before loss of capacity will continue to be used in the study. If further interventions are required, then advice will be sought from a consultee for them to continue in the study.

Northern Ireland
Those who lose capacity to consent will be treated in accordance with section 132 of the Mental Capacity Act (NI 2016). In the event that a previously consenting participant loses capacity, their statement will still stand unless subsequently withdrawn. Participants will be informed of this at the time of consent. They would continue with the study interventions unless they object.

Scotland
There is no specific legal provision for those who develop incapacity during research studies. It is generally accepted practice to inform those consenting that they will continue to be included in the study even if they develop incapacity. Participants would continue with the study interventions unless they object.

For patient participants who regain capacity to consent
Any participant who regains capacity during their hospital admission will be visited by the research team. If a participant regains capacity once discharged from hospital, they would either be able to contact the local or central research team using contact details provided to the consultee/PLR, or at the four month follow up. The study will be explained to them with an appropriate consent form and participant information leaflet. The researcher will make it clear that they do not have to continue to participate in the study but that previously collected data cannot be deleted.

NHS Staff recruited to S2
Staff recruited to the S2 survey will be recruited using implied consent. The purpose of the survey will be explained at the beginning of the survey. Potential participants are able to contact the central research team for information. Potential participants will be informed that the research team will not collect any personal, sensitive or confidential information and that they will not be identified in any outputs. This approach is taken as the burden for staff in participating is deemed to be low.

NHS Staff recruited to S3

Staff recruited to the S3 section of the project will be recruited using implied consent. This will be clearly explained verbally by the researcher administering the survey and in writing on the survey. Potential participants will be informed that the research team will not collect any personal, sensitive or confidential information and that they will not be identified in any outputs. This approach is taken as the burden for staff in participating is deemed to be low.

STUDY REGIMEN

S1: Prospective, Observational Cohort Study

Following participant consent or advice from an appropriate consultee or PLR, study data will be gathered pre-operatively and post-operatively.

Participant involvement Summary

The table below shows the maximum time that participants could be involved (if they remain an inpatient for seven days).

	Participant	Anaesthesia trainee and / or research nurses	Central team
Consent, day 0	10 min	10 min	
Frailty assessments, day 0	10 min	10 min	
Preop and postop processes, day 0		5 min	
Delirium assessment, days 1 and 3	5 min x 2	5 min x 2	
Delirium trigger words review, days 1 and 3		5 min x 2	
Postoperative morbidity score, days 3 and 7		5 min x 2	
Quality of life assessment, 4 months postoperatively	8 mins	8 mins	
Data linkage			X

Preoperative data collection

Participant characteristics

Participant characteristics will be recorded primarily through a review of the medical notes, with participant confirmation if necessary. A relative or carer would be contacted face to face or by telephone if the following criteria were met:

- The participant lacks capacity or consents to the research team contacting the specified relative or carer
- The participant is unable to confirm the details required below
- The medical notes review doesn't provide adequate information

Medical data

- Planned surgical procedure
- Urgency of surgery (emergency, urgent, expedited, planned)
- Indication for surgery: cancer / non-cancer
- Co-morbidities: defined list [APPENDIX 2] (count, total)
- Count of regular medications
- Age
- Sex at birth

- Gender
- Ethnicity
- Body mass index
- Most recent laboratory test results (within 6 weeks of admission) [APPENDIX 3]
    - Full blood count
        - Haemoglobin
        - Red cell distribution width
        - White cell count (total)
        - Lymphocyte: neutrophil ratio
    - Creatinine & electrolyte
- SARS-Cov-2 status
    - Positive (nasopharyngeal swab or high clinical suspicion of Covid-19)
    - Not positive
- Generic or surgery specific risk scores [APPENDIX 4]
    - ASA status
    - SORT version 2 score
    - Charlson Comorbidity Index

Socioeconomic data

- Source of admission [APPENDIX 5]
    - Home (including level of support)
    - Residential home / retirement complex
    - Care home
- Postcode (surrogate for socio-economic deprivation status)
- Highest education level (surrogate for a socioeconomic model): using UK Census 2011 list [APPENDIX 6]

Frailty data

Three tools will be used to assess presence and severity of frailty on admission. Two active tools (requiring participant involvement) and one passive (not requiring participant involvement) tool will be used. We anticipate frailty scoring will be carried out prior to surgery in all but the most challenging circumstances. Frailty scoring would only be carried out after surgery where preoperative frailty scoring cannot be done for participant related reasons.

The Clinical Frailty Scale (CFS) [APPENDIX 7] provides a word and pictorial representation of the frailty syndrome and is recommended in the UK as a national screening tool for frailty with prior use in surgical populations. It requires the participant (and/or family/carers) to give a history of functional status at baseline.

- Using both graphical and textual descriptors
- Completed by researcher before other frailty tools are seen to avoid confirmation bias

Reported Edmonton Frail Scale (rEFS) [APPENDIX 8] is brief, feasible and has also been used in surgical populations. The 'reported' modification of the tool will be used avoiding the need to formally assess 'timed up and go'. This tool requires participants to answer questions and draw a clockface.

The electronic Frailty Index (eFI) operationalises the deficit accumulation model of frailty but is not available in all areas of the UK. Only available for those participants registered at a GP practice that routinely collates eFI data.

The gold standard for frailty assessment is the Comprehensive Geriatric Assessment (CGA) but this is not feasible either within SNAP 3 or in routine perioperative practice.

The Hospital Frailty Risk Score can be calculated from HES data at discharge. We will report this, as it may be a useful automated method to highlight frailty to primary care colleagues.

Process of Care Data
Data on the following components of care delivery will be collected, primarily from a notes review with participant confirmation if necessary.

Preoperative care process
Model of preoperative assessment:
- None
- Nurse-led preoperative assessment
- Anaesthetist-led preoperative assessment (notes review)
- Anaesthetist-led preoperative assessment (face-to-face review)
- Physician-led preoperative assessment
- Combination of above

Postoperative care process
Modes of anaesthesia (multiple combinations allowed)
- Local infiltration only
- Regional block only
- Neuraxial block
- Sedation
- General anaesthesia with volatiles
- General anaesthesia with total intravenous anaesthesia (TIVA)

Urinary catheterisation
- None
- Catheterised pre-operatively
- Catheterised post-operatively (day 0, 1, 2 or 3)
- Long-term catheter in situ

Levels of postoperative care
- Ward
- Planned admission to Post Anaesthetic Care Unit (nurse led, protocol driven, level 2/3 care for up to 24 hours postoperatively)
- Ward with unplanned admission to critical care/ Post Anaesthetic Care Unit
- Planned admission to critical care

Outcomes

Medical complications

Length of acute hospital stay (days) will be the primary outcome as it is expected to be affected by both medical complications and discharge planning issues. The other outcomes are important either as mechanistic explanations or as complementary patient-relevant metrics. Researchers will inform the usual care team if our assessment tools reveal previously undiagnosed delirium or other comorbidities.

Delirium
- Presence or absence of delirium on either of days 1 and 3 if participant remains admitted

    - 4AT scored on days 1 & 3 [APPENDIX 10] (Total 4 or above/12) or (CAM-ICU scored on days 1 & 3 if the participant is in ICU [APPENDIX 14])
    - Review of nursing and medical notes for standard 'delirium' trigger words [APPENDIX 11]
- Total 4AT score from both days (Total 0- 24)

Postoperative Morbidity Survey (POMS) [APPENDIX 9]

- Day 3 & 7 if participant remains admitted (mainly from notes)
- Binary with domain of postoperative morbidity recorded eg. Pulmonary, renal etc
- Using specialty specific adaptations where appropriate (cardiac, hip fracture)

Death

- In-hospital (local data and data linkage) (binary)
- One year mortality via data linkage
- Two year mortality via data linkage
- Five year mortality via data linkage
- Ten year mortality via data linkage

Healthcare resource use

Length of stay

- Acute hospital stay (days)
- Days alive and out of hospital (DAOH)
    - Within first 30 and 90 days (via linkage with NHS Digital data)

Readmission within 30 days

- Routine data available from linkage with NHS Digital (binary)

Quality of life

Participant details regarding quality of life will be collected via an emailed survey or telephone survey. At the point of consent into the study, participants will specify which mode of follow up they would prefer as initial contact. Participants who opt for email follow up initially will receive up to three email reminders with an interval of one week between each. If they do not respond to those reminders, then they will receive up to three phone calls. If they don't respond to these calls then attempts to follow up will be ceased.

Discharge disposition from hospital using same definitions as for admission [APPENDIX 5]

EQ-5D-5L [APPENDIX 13]

- 4 months email/telephone follow up.
    - EQ-5D-5L descriptive system as a health profile
    - EQ VAS as a measure of overall self-rated health status
    - EQ-5D-5L index value.

Patient / carer estimate of days alive at home (DAH)

- DAH is defined as number of days in the patient's own home [i.e. not family (other than for planned holidays), rehabilitation, respite or new residential care] in the time since surgery.
- DAH has been repeatedly shown to be a preferred outcome measure for people after surgery.
- In practical terms, the data are based on the patient/carer's estimate of number of days not spent at home after discharge.

- Data for hospital admissions will be cross-checked with HES / ONS data (collected for DAOH). This will account for hospital length of stay and readmissions but residence out of hospital but not at home relies on patient report.

S2: Organisational Survey of Perioperative Care

Objective

- Describe the variation in hospital-level frailty-related interventions

Method

Survey of current arrangements for perioperative care services provided across the UK. An electronic survey will be distributed to the Principal Investigator in each hospital. Up to three reminders will be sent if the survey is not answered.

S3: Survey of referrals and interventions to general medical and geriatric medicine teams

Objectives

- Describe the involvement of general and geriatric medicine registrars in the perioperative care of surgical patients.
- Gain a brief understanding of the training that medical registrars receive in perioperative medicine.

Methods

Retrospective questionnaire study conducted with on call medical doctors. Medical registrars will be informed of the survey's purpose and data collection period prior to the start date. Anaesthetic trainees will contact the on call medical registrar and geriatrician registrar at end of day and night shift (dependent on local shift patterns) and complete the brief survey. The survey will be conducted face to face or via telephone depending on local handover arrangements. The data will be directly entered into REDCap.

The survey will take place over up to seven consecutive days. Data capture will allow responses for more than one referral per doctor. No identifiable patient data will be collected.

Pilot Study

All elements of SNAP 3 will be piloted before use in the main study. The piloting trusts will include a range of different hospitals including University teaching and district general hospitals.

- S1 will be piloted in three trusts over two days
- S2 will be piloted by a small group of perioperative clinicians
- S3 will be piloted in three trusts over five days

Patient facing documents, database use, study methods and site practicalities will be monitored, and changes made accordingly. These will be carried out approximately 2-4 months prior to the main study to allow for necessary changes to be approved by regulatory bodies.

Compliance

Data completeness will be described in all reports. The data collection tool will have forcing functions to trap erroneous data and prevent locking without completion of data queries.

Data linkage

The database will run through the research database platform, 'REDCap', an internationally recognised standard for study database management. This will be hosted on servers managed by the University of Nottingham.

Data will either be entered via the secure web-based portal onto the study database or onto a paper CRF, with later transcription. It is anticipated that local researchers will use secure hospital computers and personal devices including laptops, tablets and mobile phones to access REDCap. 'Secure' is defined as a device that is suitable for accessing NHSMail. REDCap is accessed via a web browser page; any data entered onto the page is encrypted and sent to the central server upon saving. No personal health data is retained on the device.

The minimum amount of patient identifiable data will be extracted from the study database by the central investigation team. This information will be entered, onto a password protected Excel spreadsheet, and emailed securely via NHSmail to the Public Health Authorities and Government Agencies to facilitate linkage to central held administrative and mortality data. In Wales information transfer will occur via a secure information portal:

- England- NHS Digital
- Wales- Digital Health and Care Wales
- Scotland- NHS National Services Scotland
- Northern Ireland- no central data provider, trusts will be asked to provide data individually.

The returned dataset will be directly uploaded onto REDCap to facilitate analysis. The patient identifiable data will be pseudonymised as detailed below prior to analysis by the central team. All data will be securely stored on University of Nottingham systems and access will be restricted only to those who require it.

Mortality will be tracked for all patients with a final censure date of ten years after participant recruitment. Initial data linkage will occur four months after recruitment. Subsequent data linkage requests will be made at one, two, five and ten years.

Four patient identifiers will be used: patient name, date of birth, NHS number and postcode. These fields will be used to ensure individual patient records within the SNAP 3 system are managed correctly, keeping distinct treatment episodes linked to the correct patient. The NHS number is not completely populated in the NHS Digital system and the other patient identifiers are used when the NHS number is absent. In addition, by using these four identifiers in combination, possible erroneous record linkages are flagged. Exact details of this linkage will be dependent upon the current regulations and requirement of the Public Health Authorities and Government Agencies at the time of linkage.

Among the patient identifiers, only sex will used for analysis. A pseudonymised dataset will be used by the central SNAP3 study team for analysis. In this pseudonymised SNAP3 dataset:

- The NHS number will be replaced by a unique study patient identifier.
- Date of Birth will be converted to Age on date of surgery, and trimmed to year of birth
- Postcode will be converted to ONS Lower Super Output Area, which allows the allocation of the Index of Multiple Deprivation (IMD) and the Income Deprivation Affecting Older People Index (IDAOPI).

The data items will be retained in their original format in the identifiable dataset which is retained within the SNAP 3 IT system. Fuller details of the linkage process are in APPENDIX 12.

Criteria for terminating the study

As a non-interventional study of short duration, we do not anticipate any formal stopping / termination rules. If a specific site needs to terminate recruitment or follow up for an unanticipated reason, then any data entered previously would be retained. Any unused study materials should be destroyed by the Principal Investigator of the site or his/her nominated deputy.

ANALYSES

Methods

The primary analysis will be performed by the trainee lead as part of their higher degree, in conjunction with the study statistician and the SMG. Analyses will be conducted using up-to-date versions of R and relevant packages.

To address the primary objective, we will report the proportion of frail patients, proportion of multimorbid patients and the proportion of patients experiencing post-operative delirium. Bootstrap confidence intervals will be calculated to allow for heterogeneity in the patient population.

To investigate the relationship between frailty and a range of outcomes, we will use multilevel regression models adjusting for other preoperative patient characteristics and type of surgery, with hospital-level random intercepts to control for potential between-hospital differences in outcomes. Appropriate models will be chosen for different outcome types: multilevel logistic regression for binary outcomes, multilevel quantile regression for length of stay, DAOH and DAH, and multilevel linear regression for the EQ-5D utility index.

To address the objectives relating to hospital-level and patient-level interventions and procedures designed to address risks associated with patient frailty, we will study the sample of patients identified as frail pre-operatively. We will document between-hospital differences in interventions and procedures, using descriptive statistics and graphical methods. The role of these interventions in modifying the risk of adverse outcomes in patients with frailty will then be assessed using the types of multilevel models described above, as appropriate for each outcome.

Development and internal validation of a risk prediction model for delirium will involve the following steps: (1) Exploratory and graphical analysis of the shapes of the relationships between (numeric) candidate predictors and the probability of delirium. (2) Use of fractional polynomials to identify suitable transformations of numeric predictors, as appropriate. (3) Penalized logistic regression (ridge or lasso regression) will be considered for predictor selection, since these have been shown to outperform maximum likelihood estimation and backward selection procedures in the development of risk models (van Smeden et al 2019). (4) The quality of the risk model will be assessed using the C-statistic (area under the ROC curve), which is to be estimated using optimism correction via bootstrapping (Austin & Steyerberg 2017). We will follow the TRIPOD statement (Collins et al 2015) in reporting the development and internal validation of the risk prediction model for delirium.

For all analyses, missing variable values will be investigated and described. Likely processes of missing information will be identified, and the risk of bias due to missing values assessed. If appropriate assumptions are met, multiple imputation of missing values may be employed to reduce the risk of bias due to missing values.

No interim analyses are planned.

All data will be analysed on UoN computers and backed up to the UoN servers.

Sample size and justification

The estimated sample size is around 12,000 participants based on national data (HES) and previous SNAP projects. We verified that this is a sufficient sample size to achieve the primary and secondary objectives of this study.

To estimate the proportion of frail patients, and the proportion of patients who develop delirium, a sample size of 7,203 is needed for a margin of error of 1 percentage point (width of 95 % confidence interval: 2 percentage points). This calculation is based on an outcome proportion of 0.25, which is a plausible conservative upper bound. The true proportions are likely to be smaller, which would yield better precision of the estimation of the true proportion.

To estimate required sample sizes for the delirium risk prediction model, we followed Riley et al (2020). We made the following assumptions:

- The number of candidate parameters in the risk prediction model is at most 30
- The proportion of patients with delirium is at least 0.05, and at most 0.25
- The Cox-Snell R-square of the prediction model is at least 0.05

These are conservative assumptions. Using the most conservative assumptions in each calculation, the required sample sizes for the following desirable quality criteria are:

- Mean absolute error of predicted probabilities <= 0.01: n = 11,077
- Shrinkage during model development using penalized regression methods <= 5 %: n = 5,395
- Overoptimism of model performance <= 1 %: n = 8,909

These are strict quality criteria, and they suggest that a sample size of around 11,000 patients is sufficient to estimate a high-quality clinical prediction model for delirium.

To achieve the objectives relating to hospital variation in, and effects of, processes and procedures for treating frail patients, we plan to estimate multilevel multivariate models. There is no precise method for sample size calculations for these kinds of analyses. A conservative lower bound of the percentage of frail patients in our achieved sample is 10 %, which implies a minimum sample size of 1,200 frail patients. This will give these analyses meaningful precision even in the presence of many covariates.

A priori subgroup analyses will be defined in the statistical analysis plan that will be published separately before data-lock.

ADVERSE EVENTS

The occurrence of an adverse event as a result of participation within this study is not expected and no adverse event data will be collected.

ETHICAL AND REGULATORY ASPECTS

There are three main ethical issues to address outwith the usual requirements of confidentiality throughout the process.

Collection of sensitive data
By definition, this is a study relating participants' health and social background to outcomes. Questions about health are relatively routine. We have deliberately chosen to limit the questions which relate to social background to highest level of education and postcode. Information which individuals may feel embarrassed to disclose such as occupation, household income etc. are not part of this study.

Electronic consent
Our study will pose minimal inconvenience, and no risk to participants. We will collect additional information about the participants, without changing their treatment. To reflect this, we will encourage sites to use electronic consent forms, with back up paper consent forms available. The electronic consent form (or declaration to say that paper consent has been signed) will be built into the data entry form, to ensure that investigators gain consent before moving on to collect data. Each consent declaration will be read out to the potential participant and signed with a 'simple electronic signature' tick box by the participant. At the end of the consent form, a handwritten electronic signature will be required either by using the mouse or touch screen. We will ensure that hospital level infection control processes are followed when electronic devices are handled by participants and researchers.

Time for consent
Our PPI work and previous research studies by our team and others, have shown that participants prefer a single approach and consent process without a 'reflection' time. This is a largely non-interventional study where consent for further participation (e.g. frailty and delirium assessments) will be sought verbally.

Electronic data entry
To minimise time and inconvenience for patients wishing to take part, we will encourage sites to use secure devices to directly input personal health data onto REDCap. REDCap offers a secure web-based portal where individual researchers can enter data. All precautions will be taken to safeguard patient data and ensure confidentiality. No data is stored on individual devices, it is uploaded to a secure server based at the University of Nottingham. A secure device is deemed to be any electronic device that is secure enough to access NHS email. Local researchers are only allowed to view and amend data from their own site.

Inclusion of older people and people without capacity to consent to the research study for themselves
Excluding such people from studies is viewed as discriminatory and unethical. The purpose of the study is to improve care for those with and at risk of frailty and delirium, so excluding them, or putting barriers to their participation undermines the scientific purpose of the study.

ETHICS COMMITTEE AND REGULATORY APPROVALS

The study will not be initiated before the protocol, consent forms and participant information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the

protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately, and the REC will be informed.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice and the UK Department of Health Policy Framework for Health and Social Care, 2017.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent or assent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee, and the participant or other legally authorised representative, shall both sign and date the Consent/Advice Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Study records. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the study. Consent may be carried out using electronic or paper forms.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No study-specific interventions will be done before informed consent has been obtained.

For participants unable to consent for themselves (most, but not all, of whom will be in the emergency cohort) a personal or professional consultee or PLR process will be used. If a personal consultee or PLR is available, the same process as detailed above will be followed using Consultee or PLR Information Sheets and Consultee Assent or PLR consent forms. If a personal consultee or PLR is unavailable, a professional consultee (ward / admission unit nurse or doctor) will be consulted. If the lack of capacity is temporary or intermittent every effort will be made to inform the participant and seek their retrospective consent.

Consultation and consent including a brief explanation of the study with personal consultees or PLR may be performed by telephone. This is to allow compliance with social distancing requirements. There is a guidance sheet provided for researchers asking for advice or consent over the telephone. An emailed copy of a Telephone Consultee or Telephone PLR Information Sheet will be offered to each legal representative of the participant.

The investigator will inform the participant/consultee of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Case Report Forms

Each participant will be assigned a study identity code number, for use on CRFs, other study documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mm/yy).

The electronic database held on University of Nottingham servers will identify participants by study number, be password protected, with frequent electronic and periodic physical back up. The central team will have access to all personal health data for purposes of audit, query resolution and analysis. Local researchers will have access to their own site's personal health data for the purpose of data entry.

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Study Number, to permit identification of all participants enrolled in the study, in case additional follow-up is required.

CRFs shall be restricted to those personnel approved by the Chief or local Investigator and recorded as such in the study records.

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.
The Chief or local Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, study records and field notes. A CRF may also completely serve as its own source data. Only study staff shall have access to study documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents shall be made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities.

DATA PROTECTION

All study staff and investigators will endeavour to protect the rights of the study's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The CRF will only collect the minimum required information for the purposes of the study. Where used, CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the study staff and investigators and any relevant regulatory authorities (see above). Computer-held data including the study database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).

Information about the study in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for clinical study participants and study staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but study participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance in respect of claims made by research subjects.

STUDY CONDUCT

Study conduct may be subject to systems audit for inclusion of essential documents; permissions to conduct the study; CVs of study staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, timeliness of visits); accountability of study materials and equipment calibration logs.

The Study Coordinator/Academic Supervisor, or where required, a nominated designee of the Sponsor, shall carry out a site systems audit at least yearly and an audit report shall be made.

STUDY DATA

Monitoring of study data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Study Coordinator or where required, a nominated designee of the Sponsor, shall carry out monitoring of study data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. The study database will include error trapping and verification at the point of data entry. The database is built to include a full audit trail. The local PI will verify data for 10 complete cases for each hospital site. In addition, the subsequent capture of the data on the study database will be checked. Where corrections are required these will carry a full audit trail and justification.

Study data and evidence of monitoring and systems audits will be made available for inspection by the REC as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal

Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least seven years after the end of the study or for longer if required. Any contact details obtained for participants, consultees or Personal Legal Representatives will be securely destroyed after three years. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The study documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all anonymised audio recordings, study databases and associated meta-data encryption codes.

DISCONTINUATION OF THE STUDY BY THE SPONSOR

The Sponsor reserves the right to discontinue this study at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical or personal information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the Chief Investigator and where appropriate report accordingly.

Data generated as a result of this study will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

A detailed dissemination plan will be created in conjunction with the SMG, PPI representative and the HSRC / RCoA during the course of the study. This will include at the least:

- Peer reviewed scientific publications
- Formal study report with public launch
- Clinician and lay media reports
- Slide decks for use by clinicians and researchers
- Dissemination by social media channels
- Dissemination through key professional bodies including: Centre for Perioperative Care (CPOC); Royal College of Physicians; Royal College of Surgeons; British Geriatric Society

Participants will not be identified in any publications. We anticipate dissemination of findings within 21 months of final participant involvement.

USER AND PUBLIC INVOLVEMENT

PPI has been and will continue to be embedded within the project. The study budget includes appropriate funding for PPI activity in accordance with NIHR Centre for Engagement and Dissemination guidance (2021).

Topic selection

The broad study question has been identified as a priority research question by the Priority Setting Partnership of the National Institute of Academic Anaesthesia.

The study topic itself was chosen by a panel including members of the RCoA PCPIE panel.

PPI work has been completed prior to this study looking at consent processes.

Participant / consultee information sheets have been co-produced with PPI representatives.

Two PPI/E representatives are full members of the study steering committee and the study management group. Committee chairs will be briefed to ensure that PPI/E voices are welcomed and heard at all times.

Undertaking the research

We do not anticipate asking PPI/E representatives to undertake participant recruitment or data collection. However, we anticipate active involvement of PPI/E representatives in analysis and interpretation of results. PPI/E representatives will not have access to any patient identifiable information, nor will they directly access the REDCap database.

Dissemination of the research

Members of the PPI group will be involved in dissemination in a similar fashion to the trainee lead – co-authoring, and encouragement to present (in accordance with their wishes) at meetings.

STUDY FINANCES

Funding source

This study is funded by the Royal College of Anaesthetists and the Frances and Augustus Newman Foundation.

Participant stipends and payments

Participants will not be paid to participate in the study. Travel expenses will be offered for any hospital visits in excess of usual care.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)_____

Signature:_____

Date: _____

LIST OF APPENDICES

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