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Study protocol for a national observational cohort investigating frailty, delirium and multimorbidity in older surgical patients: the third Sprint National Anaesthesia Project (SNAP 3)

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ABSTRACT

Introduction Older surgical patients are more likely to be living with frailty and multimorbidity and experience postoperative complications. The management of these conditions in the perioperative pathway is evolving. In order to support objective decision-making for patients, services and national guidance, accurate, contemporary data are needed to describe the impact and associations between frailty, multimorbidity and healthcare processes with patient and service-level outcomes.

Methods and analysis The study is comprised of an observational cohort study of approximately 7500 patients; an organisational survey of perioperative services and a clinician survey of the unplanned, medical workload generated from older surgical patients. The cohort will consist of patients who are 60 years and older, undergoing a surgical procedure during a 5-day recruitment period in participating UK hospitals. Participants will be assessed for baseline frailty and multimorbidity; postoperative morbidity including delirium; and quality of life. Data linkage will provide additional details about individuals, their admission and mortality.

The study's primary outcome is length of stay, other outcome measures include incidence of postoperative morbidity and delirium; readmission, mortality and quality of life. The cohort's incidence of frailty, multimorbidity and delirium will be estimated using 95% CIs. Their relationships with outcome measures will be examined using unadjusted and adjusted multilevel regression analyses. Choice of covariates in the adjusted models will be prespecified, based on directed acyclic graphs.

A parallel study is planned to take place in Australia in 2022.

Ethics and dissemination The study has received approval from the Scotland A Research Ethics Committee and Wales Research Ethics Committee 7.

This work hopes to influence the development of services and guidelines. We will publish our findings in peer-reviewed journals and provide summary documents to our participants, sites, healthcare policy-makers and the public.

Trial registration number ISRCTN67043129.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The breadth of UK hospital engagement and inclusivity of the study will allow conclusions applicable to countries with similarly developed healthcare systems.
⇒ Inclusion of those without capacity has been encouraged with the use of consultees, this aims to reduce sampling bias of inappropriate exclusion.
⇒ Recruitment will occur over a short period which may result in our dataset not being truly representative of the emergency surgical work carried out across the week.
⇒ We have taken a balanced approach between pragmatism and meticulous identification of outcomes by combining clinical assessment with a retrospective notes review.
⇒ There is a reasonable chance of losing participants to follow-up. We have minimised the chances of this occurring by providing email reminders to local investigators; offering email or telephone outpatient follow-up to participants and using data linkage to reduce participant burden.

INTRODUCTION

Background

The proportion of people aged 60 years or more undergoing surgery in England increased from 12.6% in 2000 to 17.8% in 2015.[1] This is due to increased longevity; patient expectations of quality and length of life increasing; and advances in perioperative medicine, anaesthetic and surgical techniques.[2]

Many older people benefit from surgery through an increase in longevity or an improvement in symptoms. Yet, among surgical patients, older age, frailty and multimorbidity are associated with higher rates of postoperative morbidity, mortality and adverse patient-reported outcomes such

as quality of life and loss of independence.[3–14] Frailty is characterised by physiological decline across multiple organ systems with multidomain loss of reserve, resulting in vulnerability to a range of adverse outcomes following a stressor event.[15] Multimorbidity is the presence of two or more coexisting chronic diseases in one individual.[16] The relationship between frailty and multimorbidity and their contribution to postoperative outcome in a surgical setting has not been thoroughly explored to date.[17]

Delirium is a state of acute confusion that is commonly reversible and is characterised by fluctuating levels of attention and awareness; disorientation; memory impairment; disturbances of perception; and disorganised thinking.[18] It is one of the most frequently occurring postoperative complications in older adults. It is commonly reversible and is preventable in approximately 40% of cases.[19 20] Occurrence of delirium is associated with increased mortality at 12 months, as well as functional and cognitive decline.[21 22]

Frailty and delirium are geriatric syndromes which commonly coexist in older patients; however, the details of their relationship are not fully understood. Those who are frail are vulnerable to minor stressors, and so might be expected to more commonly suffer with delirium and other poor outcomes.[15 23] In a study of older patients recently discharged from hospital, those who were frail were found to be 2.5 times more likely to experience delirium than the corresponding non-frail population.[24] Another study of older vascular patients found that frailty was a strong predictor for delirium with an OR of 5.66 (95% CI 1.53 to 21.03).[25] Intuitively, the presence of multimorbidity might also be expected to increase a patient's likelihood of suffering delirium. A study of older patients undergoing elective surgery found a relative risk (RR) of 1.75 for delirium in those suffering multimorbidity compared with those without.[26]

The influence of frailty on a range of patient outcomes including postoperative quality of life, mortality, morbidity, reoperation, length of stay, readmission and discharge to residential care is widely reported.[3 4 6 27–29] A review of older surgical patients by Lin *et al* demonstrated a significant relationship with 12-month mortality, finding an OR of 1.1–4.97 for those living with frailty, compared with patients who were not frail.[3 30 31] Two of the studied papers also reported an association with 2-year mortality (OR 4.01 (95% CI 2.61 to 6.16)[31]) and 5-year mortality (OR 3.6 (95% CI 2.3 to 5.5[32]). The review also highlighted an association between frailty and length of stay.[3 33–36] This association was further demonstrated in a systematic review of acute surgical patients by Leiner *et al*. In this meta-analysis, those living with frailty experienced an increased length of stay with a weighted mean difference of 4.75 days (95% CI 1.79 to 7.71, p=0.002).[28] A further meta-analysis by Panayi *et al* found that surgical patients living with frailty were more likely to experience postoperative complications (RR of 1.48, 95% CI 1.35 to 1.61, p<0.001), readmission (RR of 1.61, 95% CI 1.44 to 1.80, p<0.001) and discharge to skilled care (risk ratio of 2.15, 95% CI 1.92 to 2.40, p<0.001).[29]

Routine assessment and management of frailty, multimorbidity and risk of postoperative delirium can reduce the likelihood of adverse outcomes in older patients.[2 27 37] In recent years, the specialty of perioperative medicine has brought together physicians, geriatricians, anaesthetists, surgeons, nurses and allied healthcare professionals, to enhance preoperative assessment; management and postoperative care of these patients. However, the provision of this skilled and specialised service differs across the UK with the varying degrees of resource allocation, local enthusiasm and operational priorities. Furthermore, surgical pathways are heterogenous, often combining proactive and reactive services led by different specialities. The criteria for accessing perioperative medicine services are diverse, based on age, clinical need, surgical specialty, surgical procedure and clinician preference.[37–40]

There is no single metric that defines a 'good' outcome following surgery. Length of hospital stay as a metric of outcome has been criticised due to the influence of social and organisational factors. However, these factors are associated with frailty and multimorbidity, and furthermore are important metrics at an organisational and financial level in particular due to an ageing surgical population and resource constraints within healthcare.

In order to support objective decision-making for individual patients, services and national planning, accurate, granular and contemporary data are needed describing the impact and association among frailty, multimorbidity and processes of care with patient and service-level outcomes.

This study is called the Sprint National Anaesthesia Project 3 (SNAP 3). We have designed it to describe the incidence of and relationships among frailty, multimorbidity and postoperative delirium in the older surgical patient. This protocol will be used across participating UK hospitals. Further research using an adapted SNAP 3 protocol is planned in Australia. From our results, we hope to provide suggestions for the future development of perioperative care for the older surgical population.

Objectives

To describe the impact of frailty, multimorbidity and delirium, and their management, on outcomes following surgery in patients aged 60 years and older undergoing surgery.

Primary objective:

- Objective 1: To describe the prevalence of frailty and multimorbidity and the incidence of postoperative delirium in a surgical population aged 60 years or more.

Secondary objectives:

- Objective 2: To describe the bivariate associations between our three main variables of interest—frailty, multimorbidity, delirium—with a range of patient-related and process-related outcomes.

- Objective 3: To describe the bivariate associations between frailty and delirium, as well as multimorbidity and delirium, where delirium is viewed as an outcome.
- Objective 4: To provide an estimate of the effects of frailty, multimorbidity and delirium on primary and secondary outcomes with adjustment for clinically important confounding factors including surgical specialty, surgical acuity and surgical complexity.
- Objective 5: To establish the degree of agreement among three measures of patient frailty: Clinical Frailty Scale (CFS), Reported Edmonton Frailty Score (rEFS) and Electronic Frailty Index (eFI).
- Objective 6. To estimate the proportions of patients who receive more in-depth perioperative interventions, separately for those identified as frail when compared with patients not identified as frail.
- Objective 7: To develop and internally validate a risk prediction model for postoperative delirium.
- Objective 8: To describe the national provision of perioperative medicine services for older people.
- Objective 9: To identify associations between perioperative medicine for older people services and primary and patient-reported secondary outcomes.
- Objective 10: To estimate the acute, unplanned workload for general and geriatric medicine registrars generated by acute referrals for older surgical patients.
- Objective 11: To identify associations between hospital-level perioperative medicine services and the workload from surgical patients referred to general and geriatrician medical registrars.

METHODS

Study design and setting

The SNAP 3 programme of work consists of a study (S1) and two surveys (S2 and S3) to be conducted in participating hospitals across the UK:

S1. A 5-day, prospective, observational cohort study of those who are 60 years and older, undergoing surgery to describe incidence, relationships and outcomes related to frailty, multimorbidity and postoperative delirium.

S2. Organisational survey regarding the provision of perioperative medicine facilities for older surgical patients.

S3. An observational, cross-sectional survey of acute referrals from surgical specialities to medicine and the provision of perioperative medicine training.

This protocol will be used in all participating UK sites and has been received favourable opinion from the relevant ethics committees. The study will be replicated in Australia. Due to differing regulations surrounding research, the protocol will be adapted for local implementation outside of the UK, and this adaptation will be published separately. Our approach is modelled on the Donabedian framework of structure, process and outcomes.[41] The methodology of the cohort study will be discussed in full below.

Organisational survey S2

Each site participating in SNAP 3 will be asked to complete an organisational survey.

This will describe the provision of perioperative medicine services at hospital level. We hope this information will illustrate the range of perioperative medicine services and the differing criteria used to access such services in different centres. One survey is requested per hospital site via the principal investigator who could delegate the responsibility to a more appropriate individual if necessary.

Medical registrar survey S3

For a minimum of 24 hours, each general and geriatric medicine registrar (including middle grade trainee or Trust grade equivalents) providing acute medical cover will be asked to complete a survey on the workload resulting from older surgical patients. The survey will describe brief details of the medical problem, the nature of the review/advice given and any perioperative medicine training they have received. The objective of this survey is to quantify the unplanned workload experienced by general medical registrars and describe associations between existing perioperative medicine services and burden on acute medical services.

Outcome measures

SNAP 3 aims to detect outcomes relevant to professionals, patients and their relatives. We have used multilevel outcome metrics to capture a breadth of informative outcome markers.

Our primary outcome measure is length of stay in hospital after surgery, a well-recognised measure of importance to healthcare services and patients. We recognise that length of stay is influenced both by medical complications and discharge planning issues, both are relevant to frailty, multimorbidity and delirium. A strength of the study is the measurement of outcomes of importance to patients; days alive at home (DAH), days alive out of hospital (DAOH) and quality of life (measured by EQ-5D-5L and EQ Visual Analogue Scale (EQ-VAS)).

Secondary outcomes

Secondary outcomes are important as complementary patient or process-relevant metrics. These have been categorised into patient-related and process-related outcomes, with some crossover between these categories.

Patient-related secondary outcomes

- Delirium incidence during the first 7 days postoperatively; measured using 4AT or Confusion Assessment Method for the intensive care unit (CAM-ICU), and retrospective notes review mapped to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria for diagnosis of delirium.[18 42–44]
- Morbidity on postoperative days 3 and 7; measured using the Postoperative Morbidity Survey (POMS).[45–47]
- Mortality in hospital and at 1, 2, 5 and 10 years postoperatively.

- Quality of life at 4 months postoperatively (measured using the EQ-5D-5L, EQ-VAS).
- DAOH and DAH.[48]

Process-related secondary outcomes

- Number of referrals to acute medical services for older surgical patients, and the rate of such referrals by size of hospital (determined by number of beds).
- Readmission within 30 days of index surgical procedure, estimated using routinely collected hospital data (eg, Hospital Episode Statistics (HES) in England).

Eligibility criteria

Hospital level

All National Health Service (NHS) hospitals in the UK which carry out adult surgery (inpatient, day surgery or both) will be eligible to take part. Hospitals will be recruited through the National Institute of Academic Anaesthesia's Quality Audit and Research Coordinator (QuARC) and national research and innovation networks. The QuARC network consists of one or more research-interested/audit-interested anaesthetists in every NHS hospital who act as a contact, and in many cases also as the local lead investigator for Health Services Research Centre (HSRC) projects. There is also a national network of research and innovation support in the UK NHS, which facilitates research support for eligible studies. As a consequence, in previous HSRC-affiliated projects, there has been near complete recruitment of eligible UK hospitals.[49] We aim to recruit>95% of eligible NHS hospitals for SNAP 3, but accept that this may be challenging due to the impact of SARS-CoV-2 on workforce and theatre operating.

Patient level

Our inclusion criteria are deliberately broad, with the intention of including almost all patients who have surgery with a significant physiological stress response that could result in postoperative delirium or morbidity. Our exclusion criteria are limited and aim to minimise recruitment of participants whose clinical course is unlikely to provide information which answers our research questions.

Inclusion criteria

Patients aged 60 years or older undergoing surgery during the recruitment period are eligible for this study. Surgery includes day case, emergency and elective procedures that require general, neuraxial, regional or local anaesthesia.

Exclusion criteria

We will exclude patients undergoing invasive procedures that are diagnostic or likely to cause minimal physiological stress response, for example, endoscopy, phacoemulsification, percutaneous tracheostomy insertion. Patients with American Society of Anesthesiologists Physical Status Score grade VI are also excluded. See online supplemental file 1 for examples of included and excluded surgical procedures.

Data collection and follow-up procedures for the cohort study

Recruitment for the SNAP 3 observational cohort study will occur over a period (Monday–Friday). The majority of sites are expected to recruit in the main recruitment window in March 2022. Allowance has been made for sites unable to recruit in the March window to recruit within 2 months. If we are unable to achieve our recruitment target, ethical approval has been given for a second recruitment period. Follow-up involving direct participant contact will occur up to 4 months postoperatively. Data linkage with hospital records and Office for National Statistics (ONS) death registrations will be carried out at 120 days after discharge and at 1, 2, 5 and 10 years postoperatively.

All sites will use an electronic case report form (CRF) via a secure web-based portal 'REDCap'. An initial CRF record will be completed for each participant during the study week. The CRF includes routinely collected demographics, medical history, surgical information, blood laboratory data, SARS-CoV-2 status, surgical risk scores, socioeconomic data and frailty assessments. Please see online supplemental file 2 for details of the data points collected.

There are two active frailty tools that require participant involvement and one passive frailty score. The CFS and the rEFS are both brief and validated methods that do not require specifically trained personnel to accurately assess frailty. The eFI operationalises the deficit accumulation model of frailty but is not available in all areas of the UK. It is calculated from primary care data. The eFI will be recorded if it has been routinely collected. Those carrying out frailty assessments were given details of relevant online training modules.[50 51] The conventional cut-off values for frailty will be used in analyses. Frailty will be identified as CFS≥5, rEFS≥8 and eFI≥0.25.[27 52 53] The choice of frailty tools aims to first, accurately measure frailty in this sample and second, describe the routine usage of different frailty tools across the four nations of the UK.[52–58]

Process of care data will be recorded regarding the nature of preoperative assessment, anaesthesia type, catheterisation and postoperative care level.

Multimorbidity is assessed through a list of relevant comorbidities which has been derived from the Charlson Comorbidity Index and a priori knowledge of comorbidities relevant to older patients with frailty and at risk of delirium.[59] The Elixhauser Comorbidity Index will be calculated from HES data (or equivalent) following the method of Pritchard *et al* including a 1-year look back.[60]

Participants who remain inpatients on days 3 and 7 will be assessed for postoperative morbidity using an appropriate specialty specific POMS and either the 4AT (if not critically ill) or CAM-ICU (if critically ill).[44–47 61] Delirium and postoperative morbidity will be assumed absent for those discharged alive on the day of surgery.

Those admitted for one or more nights will have a retrospective notes review to identify delirium with the aim of minimising false negatives from researcher

assessments alone. This will include medical and nursing documentation, from the day of surgery, up to discharge or day 7 postoperatively, whichever is sooner. A tool has been developed to enable objective researcher-led retrospective notes evaluation. The tool was developed using DSM-5 criteria for a diagnosis of delirium based on literature review and a priori knowledge of language used by clinicians to describe delirium.[62–67] Each diagnostic criterion from DSM-5 has been mapped to a set of words and phrases which are commonly used to describe that specific clinical feature.

We aim to minimise the number of missed delirium episodes by combining the findings of the notes review and POMS with either the 4AT or CAM-ICU. This pragmatic approach to the identification of delirium is proposed due to the inherent difficulty in measuring a fluctuating condition with limited resource.

Quality of life will be assessed via email or telephone follow-up at 120 days after surgery. The mode of follow-up is determined by the participant or their representative. If a participant or their representative has opted into both email and telephone follow-up but does not respond to email, the local investigator will be emailed to prompt a telephone call. The EQ-5D-5L and EQ-VAS are validated tools that do not require specific training for accurate use.[68] We will also determine the 'DAH' and 'DAOH' at 120 days as a measure of the process of recovery that has been shown to be of importance to patients.[69] Days alive and out of hospital is available from central records, and hence easier to collect at scale, but excludes time in residential or nursing home care, outcomes which are often feared by older patients. DAH is more difficult to capture, but more closely aligns with what patients want from a good recovery. A possible by product of the study is a demonstration of whether the collection of DAH is worth the additional research burden.

Data linkage via national government held and hospital-level datasets will enable us to provide more detailed outcome data without further patient or local investigator burden. We will collaborate with NHS Digital, Digital Health and Care Wales, Electronic Data Research and Innovation Service, National Services Scotland and individual Northern Irish hospitals to provide as much of the long-term outcome data as possible. Due to individual countries differing legislation and record keeping, data obtained will vary across the devolved nations.

Data collection for the clinician surveys

The organisational survey, S2, will be distributed via email with a direct link to the REDCap data entry portal. S3 will be administered by researchers (anaesthetists, physicians or research nurses), who will contact medical registrars at the end of an on-call shift. This may be done over the telephone or face to face. The researcher will input their answers directly into REDCap. There will be no ongoing follow-up of clinicians.

Analysis plan

Study cohort

Descriptive statistics will be used to describe the basic demographics of our participants and key features of our participating sites.

Missing data

As with any large study with multiple follow-up surveys, there will be missing data. The number and proportion of missing observations will be documented in each analysis. For each variable, we will assess the likely process that led to missing data, to determine whether the data are missing at random or not missing at random. This will determine the choice of an appropriate method of dealing with missing data, for example, multiple imputation.

Analysis per objective

Objective 1: estimating the incidences of frailty, multimorbidity and postoperative delirium

We will estimate the incidences of our three target variables as the proportion of patients living with frailty and/or multimorbidity and who experience delirium, respectively. We will calculate 95% CIs using the binomial distribution. We will conduct sensitivity analyses with inverse probability weights for elective and emergency procedures in order to account for the absence of weekend data. We have already obtained estimates of the number of elective and emergency procedures carried out at weekends from selected hospitals and will use those to estimate the inverse probability weights.

Objective 2 and 3: univariate analyses

The relationships among frailty, multimorbidity, delirium, primary and secondary outcomes will be reported with appropriate models chosen for different outcome types: multilevel logistic quantile or linear regression. We will account for clustering of patients in hospitals through a random effect for hospitals within mixed effects models.

Objective 4: multilevel regression models

To investigate the relationships among frailty, multimorbidity, delirium and a range of outcomes, we will use multilevel regression models adjusting for other clinically relevant 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. Prior to conducting these analyses, we will draw directed acyclic graphs to clarify hypothesised causal relationships and to inform choices of potential covariates that should be included, or indeed excluded, from our models.

Objective 5: agreement between frailty tools

The analyses for objectives 1–3 will be reported separately for the different frailty measures to gauge differences

in their performance as predictors of outcome, using a range of measures of performance as appropriate for the measurement levels of the various outcomes.[70] We would not do the same for the multivariable analyses specified to address objective 4. We will measure the pairwise consistency between the three frailty measures using Spearman's correlation coefficients. To gauge agreement of clinical judgement in practice, we will also assess agreement between dichotomised versions of the three frailty measures, using their respective conventional cut-offs. Agreement between dichotomised frailty measures will be assessed via percentage agreement and kappa coefficient.

Objective 6: descriptive statistics of interventions

To address the objectives relating to hospital-level and patient-level interventions and perioperative care designed to address risks associated with patient frailty, we will study the sample of patients identified as living with frailty preoperatively and compare them to those identified as not frail. We will document between-hospital differences in interventions and procedures, using descriptive statistics and graphical methods.

Objective 7: risk prediction model for delirium

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, identified from previous studies and clinical insight, and the probability of delirium. (2) Use of fractional polynomials or splines to identify suitable transformations of numeric predictors, as appropriate. (3) Penalised logistic 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.[71] (4) The discrimination 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.[72] We will also calculate the Brier score and investigate model calibration, using graphical displays and the Hosmer-Lemeshow goodness-of-fit statistic. We will follow the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis statement in reporting the development and internal validation of the risk prediction model for delirium.[73]

Objective 8: descriptive statistics of hospital-level models of perioperative care

The national provision of hospital-level perioperative medicine services will be described. The description will be subdivided into care for elective and emergency patients; and degree of preoperative and postoperative services.

Objective 9: associations between in-depth perioperative interventions and outcomes

The role of in-depth perioperative interventions in modifying the risk of adverse outcomes in patients with frailty will then be assessed using appropriate mixed effects models as for objective 4. Patient-level covariates, such as age, socioeconomic status etc, will be included as appropriate to distinguish the influence of population characteristics with hospital-level perioperative interventions. Although there is inevitably a risk of significant unmeasured confounding, it is difficult to estimate the direction or magnitude of these effects.

Objective 10: acute referrals to medicine from older surgical patients

Descriptive statistics will be used to describe the number and nature of acute referrals to medicine from older surgical patients, and the rate of such referrals by size of hospital (determined by number of beds). The nature of the referrals will be reported as resulting in a telephone or face to face consultation. Referrals will be categorised by surgical specialty, urgency of surgery and primary medical problem.

Objective 11: identify associations between perioperative medicine services and acute referrals of older surgical patients to medicine

To describe the associations between perioperative medicine services and acute referrals of older surgical patients to medicine, we will use mixed effects logistic regression. Patient-level covariates will be included as appropriate to distinguish the relevant perioperative services. Emergency surgery patients will not benefit from an elective perioperative medicine service and so will be analysed separately.

Subgroup analyses

Data will be reported according to prespecified subgroups for objectives 1–6. Exact details of subgroups will be finalised once the numbers of patients in potential groups is known. At a minimum, the following groups will be reported:

- Emergency and elective procedures.
- Surgical invasiveness (using the method described by Abbot *et al*[74]).
- Major surgical specialty (eg, orthopaedics, gynaecology).
- The 10 most common healthcare resource groups.

Relevant subgroups will be analysed if they include at least 500 participants.

Additional analyses and data sharing

Investigators from outside the core study team may wish to conduct secondary analysis of the data from SNAP 3. We recognise the importance of sharing data within the ethical and legal constraints of the original participants' consent, in order to maximise the potential of our dataset. Following a formal request for data sharing, the request will be considered by the SNAP 3 study management group (SMG) and steering committee. If the request is made after the relevant groups have been disbanded, then the request will go directly to the chief investigator who will consider the request alongside the executive management board of the HSRC.

There are many potential further analyses possible from the SNAP 3 dataset. We anticipate developing and validating a multimorbidity score for our population. This will then be compared with other measures of multimorbidity to evaluate its ability to predict primary and secondary outcomes. Our secondary analysis plans will continue to evolve as we understand the potential of our cohort's data.

Sample size calculation

Prior to the SARS-CoV-2 pandemic, the estimated achievable sample size for the observational cohort study was around 12 000 participants based on English 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. This estimate has been reduced to 8000, in light of the impact of the pandemic on health services.

To estimate the proportion of patients living with frailty, and the proportion of patients who develop delirium, a sample size of 7203 is needed for a margin of error of 1 percentage point (width of 95% CI: 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 greater precision of the estimation of the true proportion.

To estimate required sample sizes for the delirium risk prediction model, we followed methods published by Riley *et al*.[75] 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^2 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 penalised regression methods≤5%: n=5395.
- Overoptimism of model performance≤1%: n=8909.

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 patients with frailty, we plan to estimate multivariate mixed effects models. There is no precise method for sample size calculations for these kinds of analyses. A conservative lower bound of the percentage of patients with frailty in our achieved sample is 10%, which implies a minimum sample size of 1200 patients with frailty. 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.

ETHICS AND DISSEMINATION

The study has received the following approvals: Scotland A Research Ethics Committee and Wales Research Ethics Committee 7. Ethical approvals are obtained at national level. Local confirmation of capacity and capability is provided by individual hospitals before study commencement.

Patient consent

All patients who are eligible for SNAP 3 inclusion will have capacity to consent assessed. Those who have capacity to consent to study participation will provide electronic or written consent after being provided with the participant information sheet.

It is essential to include participants without capacity to consent to study participation in order to minimise sampling bias due to exclusion of the target population. The objectives of SNAP 3 relate directly to patients who have both acute and chronic cognitive impairment. This study is of low participant burden and the new knowledge generated will improve care for those without capacity. We will use the process of consultees (in England, Northern Ireland and Wales) and personal legal representatives (in Scotland) giving advice or consent, respectively.

Patient participants who lose capacity to consent

We anticipate that a proportion of participants will lose capacity to consent during the study, most commonly due to delirium. While it is vital to continue including these participants to fulfil our research objectives, their continued inclusion is complex, and procedures vary depending on the country.

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 and Scotland

Those who lose capacity to consent in Northern Ireland 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. In 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.

Regardless of capacity, if a participant is distressed by ongoing inclusion in the study, then they will be withdrawn from the study.

Study management

The SMG is chaired by the Chief Investigator and meets at least monthly, to direct day-to-day running of the project. The SMG members include those with clinical roles in anaesthesia and geriatrics, a statistician, research management and patient and public involvement (PPI) members. The study steering committee (SSC) meets at least annually to supervise the conduct of the research and its progress achieving the study's objectives while working to the protocol. We are fortunate to have multidisciplinary input from all interested clinical groups and lay representation. We are responsible to the HSRC executive management board.

Patients and public involvement

The topic for SNAP 3 was selected through a competitive process of submissions open to all anaesthetists across the UK. The panel for project selection included representatives from PPI groups, Royal College of Anaesthetists staff, clinicians and trainees.

Our PPI members have provided valuable input into the design and conduct of the study via the SMG and the SSC. They have been influential in the selection of outcome measures especially relating to quality of life. Our PPI members have directly contributed to the format and wording of the patient facing documentation and communication with sites. They have also provided guidance on the acceptability of our study design in relation to participant burden. PPI members will be involved in the publication of our results through our dissemination plans and the production of future public facing documents.

Dissemination

We intend to present the results via our website (hosted by the HSRC), in peer-reviewed journals and through conference presentations. We will provide relevant summary reports for the following groups:

1. Our participants—participants will be offered the opportunity to receive summary findings up to 3 years after recruitment.
2. Our recruiting sites—all sites can receive an overall summary and can request a hospital specific summary.
3. Healthcare policy-makers—this will include medical and nursing royal colleges, specialist societies, department of health, NHS England, NHS Wales, NHS Scotland and Health and Social Care Ireland.
4. The public—relevant patient groups and charities will be informed of our results with the assistance of our PPI members.
5. Participating NHS Trusts and Health Boards—all NHS chief executives will receive a summary of the key findings.

All collaborators who recruit or collect data from participants, or complete clinician surveys, will be acknowledged in the manuscripts that arise from this study. Full details can be obtained on our website.

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Contributors IKM initiated the collaborative project; is guarantor; the grant holder; revised the draft paper; cowrote the analysis plan and is analysing the data. CS obtained ethical approval; implemented the study in the UK; designed the data collection tools; monitored data collection for the study; cowrote the statistical analysis plan; cleaned and is analysing the data; and drafted and revised the paper. PM provided statistical expertise in study design and cowrote the analysis plan. JP provided expertise in geriatric medicine; designed data collection tools and revised the draft paper. TP implemented the study in Australia; designed data collection tools and revised the draft paper.

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