Development and **E**valuation of **S**trategies to **I**mprove **S**edation Quality in In**T**ensive Care (**DESIST study**)

TRIAL ANALYSIS PLAN

Version 1.0; February 18th 2015

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Statistical Analysis Plan

Development and Evaluation of Strategies to Improve Sedation Quality in InTensive Care (DESIST study)

Version: 1.0

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Approval signatures

The following individuals, by providing their signatures, indicate their approval of the planned analysis as specified in this document.

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Abbreviations / Glossary of Terms

ICE-Q	Intensive Care Experience Questionnaire
ICU	Intensive care unit
IES-R	Impact of Events Scale - Revised
NG	Naso-gastric
RI	Responsiveness Index
SICSAG	The Scottish Intensive Care Society Audit Group
Pre-intervention	45 week period before implementation of interventions in any study site
Implementation	8 week period during which Education intervention is scheduled for implementation and Responsiveness Monitoring and / or Process Feedback are scheduled for implementation in ICUs randomised to receive these interventions
Post-implementation	45 week period following the Implementation phase
DESIST care period	12 hour care period corresponding to a nursing shift

Primary Objective

To explore the effectiveness of three interventions on sedation quality in mechanically ventilated intensive care patients, and any interaction between the interventions.

The three interventions studied are:

1. A web-based modular educational resource the "DESIST educational package" targeted primarily at nursing staff. This intervention is termed **"DESIST education".**
2. Feedback of process measures developed to capture relevant aspects of sedation quality in the form of "process control" charts. This intervention is termed **"DESIST process feedback".**
3. The introduction of a new sedation monitoring system into the intensive care unit (ICU), which continuously monitors patient responsiveness with the intention of alerting staff to "unresponsive" patients who are at highest risk of deep sedation. This intervention is termed **"DESIST responsiveness monitoring"**

Secondary Objectives

1. To evaluate the effect of the three interventions on the incidence of pre-defined sedation-related adverse events
2. To evaluate the effect of the three interventions on the use of intravenous sedative drugs
3. To evaluate the effect of the three interventions on the use of intravenous analgesic drugs
4. To evaluate the effect of the three interventions on the duration of mechanical ventilation during intensive care stay
5. To evaluate the effect of the three interventions on the duration of ICU and hospital stay
6. To evaluate the effect of the interventions on ICU and hospital mortality
7. To evaluate the effect of the interventions on patient experience and memories among ICU survivors
8. To evaluate the effect of the interventions on patient symptoms of hyperarousal, intrusion, and avoidance in relation to their ICU stay during the early period following ICU discharge.
9. To evaluate the effect of the DESIST education intervention on core nursing knowledge relevant to sedation.
10. To understand the factors that limited or facilitated implementation of each of the interventions

Overview of DESIST research programme

The DESIST sedation quality improvement programme included several stages that underpinned the DESIST trial.

STAGE ONE: DEVELOPMENT OF SEDATION QUALITY ASSESSMENT TOOL (SQAT)

This stage used a review of existing tools, focus groups, and an iterative process to develop a single simple checklist that captured fields relevant to assessing pain, agitation, and sedation for each 12

hour care period (typically an ICU nursing "shift"). The face and criterion validity were assessed using focus groups and comparisons with existing tools. Reliability was assessed using comparisons between two bedside nurses and between a bedside nurse and researcher, and responsiveness was assessed during episodes of chest physiotherapy. A pre-defined protocol for this stage and a separate analysis plan was developed, and the results are reported separately. See: "**Development and validation of sedation quality assessment metrics for driving quality improvement through process control methodology."**

The tool developed was used to generate the measures of sedation quality used as outcomes in the trial, and is termed the **"SQAT"**

STAGE TWO: DEVELOPMENT OF RELEVANT SEDATION-RELATED PATIENT PROCESS MEASURES

For the DESIST trial we developed sedation-related measures intended to quantify the prevalence of patient pain/discomfort, agitation, and deep sedation. The unit of time chosen was a 12 hour care period corresponding to a nursing shift. This unit of care is termed the **"DESIST care period".** The SQAT was developed to capture the relevant fields to enable measures of pain/discomfort, agitation, and deep sedation to be quantified and developed into measures that acknowledged and enabled adjustment for the need for deep sedation for certain conditions (for example: advanced ventilation strategies, therapeutic hypothermia, brain injury). SQAT fields also enabled relevant denominator data to be captured, for example ventilation status and presence of coma despite not receiving sedatives, to censure patients from the process measures where appropriate. Based on the SQAT fields, an iterative process was used to develop a number of process measures that demonstrated reliability, construct, and face validity. The final measures chosen were:

1. Proportion of DESIST care periods with patient agitation
2. Proportion of DESIST care periods with excessive sedation
3. Proportion of DESIST care periods with poor relaxation
4. Proportion of DESIST care periods with poor ventilator synchronisation
5. Proportion of DESIST care periods with optimum sedation[#]

[#]Optimum sedation was defined as a DESIST care period where none of patient agitation, excessive sedation, poor relaxation, or poor ventilator synchronisation were present

To reduce random variability we combined all data for 2 month periods from each ICU to generate the proportion of DESIST care periods for which each of the five sedation-related measures were present. Process charts were constructed that included upper and lower warning and control limits. SQAT data were collected during a 45 week pre-intervention phase in each ICU, during an 8 week implementation phase for the intervention(s) allocated to the ICU, and during a 45 week post-intervention phase. For the ICUs randomised to receive the DESIST process feedback, run charts were constructed to describe the process occurring during the pre-intervention phase. All DESIST care period data were uploaded into the trial data base, and programmes written to automate process chart generation. During the post-implementation phase process chart reports and presentations were fed back to the ICUs to illustrate changes in the processes every two months

with an updated process measure based on new data obtained during the previous two month epoch.

In addition, all pre-specified sedation-related adverse events were uploaded into the trial database in real time on receipt of completed case record forms. These data were used to generate G charts documenting the numbers of patients treated without a sedation-related adverse event. Warning and control limits for these charts were calculated, and the charts fed back to those ICUs allocated to the intervention as part of the two-monthly report. Total adverse events were also tabulated in these reports.

The development of each process measure, the algorithms used to generate them for the SQAT and DESIST care periods, and illustrative data from the pre-intervention phase of the trial are reported separately: See: **"Development of process control methodology for tracking the quality and safety of pain, agitation, and sedation management in critical care units."**

The metrics developed to describe sedation quality were used as outcomes in the trial.

STAGE THREE: DEVELOPMENT OF AN EVIDENCE-BASED EDUCATIONAL PACKAGE FOR IMPROVING SEDATION MANAGEMENT IN INTENSIVE CARE UNITS

A bespoke modular education package was developed in collaboration with an NHS provider of web-based educational materials (LearnPro NHS: http://www.learnpro.co.uk). This included in-built assessment to ensure acquisition of core knowledge across a range of relevant domains, and logging of completion. Each ICU developed strategies aimed at achieving high rates of completion during the implementation phase of the trial.

A nested sub-study used 10 questions to assess core knowledge prior to undertaking the education package. Staff were asked to complete the same core knowledge test towards the end of the implementation phase of the trial.

The DESIST education package, and the impact on core knowledge, will be described according to the analysis plan set out in this document (see below). However, these data will be reported in a separate report/publication to the main analysis: See: **"The effect of a web-based e-learning education package on sedation knowledge among intensive care nurses".**

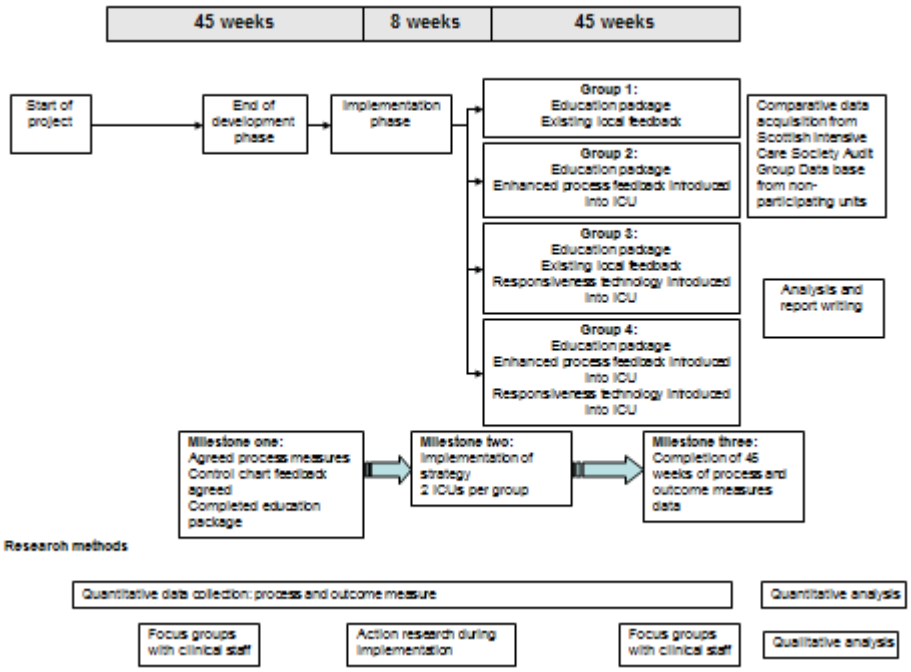
STAGES FOUR AND FIVE

Stage four comprised collecting pre-intervention data during a 45 week period in each of the 8 participating ICUs. In stage five, ICUs were then randomised to a combination of intervention(s), and an 8 week implementation period was initiated according to a pre-defined strategy. Data were subsequently collected during a 45 week post-implementation period. Figure 1 shows the general structure of the trial.

General Approach

DESIST is a quality improvement trial. The hypothesis is that the interventions used within the ICUs will result in practice changes which themselves will result in improvements to the primary and secondary outcome measures. The effects observed on the outcome measures will result from the interventions implemented in the ICUs plus the way these interventions changed practice. Consistent with the recommendations of the MRC complex intervention framework and the CONSORT guidance for reporting trials of interventions involving multiple elements, we will include a process evaluation. A key goal of the process evaluation will be to understand whether the interventions were implemented as planned, the barriers to implementation, and factors that worked well/less well. The cluster design of DESIST makes this of particular relevance; we plan *a priori* to compare effects between ICUs that process evaluation indicated successful implementation versus those in which implementation was less successful/unsuccessful. Our analysis strategy is therefore a mixed methods approach in which we primarily use a quantitative evaluation with qualitative data used to provide context and explanation of the findings.

Figure 1: The general structure of the data collection and timing of the interventions



This statistical analysis plan outlines the quantitative and qualitative analyses to be performed on the data from Stages Four and Five of the DESIST research programme.

Overall statistical principles

The analysis population will be based on the intention to treat principle and will include all ICUs included in the study and as far as possible, all consented patients from within each ICU. The exception is that patients admitted with a diagnosis of status epilepticus will be excluded from all analyses: these cases, although relatively rare (about 1% of admissions), require more complex and

individualised sedation management and so could confound the outcome measures of interest in DESIST. Throughout an overall significance level of 5% (two-sided) will be used with a particular emphasis on the use of 95% confidence intervals in the estimation of effect sizes.

The planned analyses will be performed using the STATA, MLWin and SAS statistical software.

Statistical Methods section from the protocol

Primary outcome analysis
For the primary outcome of % of ventilated patient days with optimal sedation, the following comparisons will be made based on all the data gathered:

I. ***Effect of responsiveness technology*** *- 4 ICUs implementing (sites 5,6,7,8) versus 4 ICUs not implementing (sites 1,2,3,4) in the intervention phase*

II. ***Effect of process feedback*** *- 4 ICUs receiving feedback (sites 3,4,7,8) versus 4 ICUs not receiving feedback (sites 1,2,5,6) in the intervention phase*

III. ***Interaction between responsiveness technology and process feedback*** *–any additional effect observed in the intervention phase (in sites 7,8 versus sites 1,2,3,4,5,6)*

IV. ***Education***

Comparisons I, II and III will be made within a single model incorporating all of the patient data gathered, generating estimates of the effects of responsiveness technology, process feedback and any interaction between these effects. Comparison IV will be made in a second model based on the baseline and post-implementation data from ICU sites 1 and 2.

The analysis will be performed within a (multilevel) normal linear mixed modelling framework. This will allow adjustment for the baseline covariates at both the ICU and individual patient levels. Baseline data from each study site will be included in the model to allow adjustment for between site differences in practice at baseline. As the % of patient days with optimal sedation will be based on different numbers of days for each patient, inclusion of a weighting factor to account for this in the model will be considered in a sensitivity analysis. The denominator for the % of patient days with optimal sedation will include only days on which the patient was ventilated at the time of primary outcome assessment. Subsequent ventilation days, should a patient have been readmitted to ICU within the same hospital admission, will be included in the denominator.

Hypothesis testing will be performed at the conventional 2-sided 5% significance level and considerable emphasis will be placed on estimation of effect sizes using 95% confidence intervals.

The balanced factorial nature of the design in the implementation phase enables all of the intervention phase data to be used to evaluate the process feedback and responsiveness technology interventions. For example, within the 4 ICUs implementing the responsiveness technology, 2 will be receiving process feedback and 2 will not. The same applies to the 4 ICUs not implementing the

responsiveness technology, and so the evaluation of the responsiveness technology intervention is not confounded by the process feedback intervention.

Secondary outcome analyses

Number of ventilation days, ICU stay duration, number of days on sedation will be analysed using survival analysis methods, to account for the censoring which may occur: ventilation, ICU stay and sedation may be completed due to improvement in the patient or censored if they terminate due to the death of the patient. Consideration will be given to the best approach for handling data from patients who have repeated periods of ventilation, ICU stay or sedation within a single hospital admission. Specifically, recurrent event survival analysis models will be investigated. Total sedative use will be analysed in a similar manner to the primary outcome, using multilevel normal linear mixed modelling. We will also explore changes in the process measures selected as quality measures between groups.

Outcomes

Primary outcome

Proportion of DESIST care periods with optimum sedation

Secondary outcomes

A. Primary outcome sedation quality components

1. **Proportion of DESIST care periods with patient agitation**
2. **Proportion of DESIST care periods with excessive sedation**
3. **Proportion of DESIST care periods with poor relaxation**
4. **Proportion of DESIST care periods with poor ventilator synchronisation**

B. Patient-level sedation outcomes

1. Number of DESIST care periods with optimum sedation per mechanically ventilated patient
2. Number of DESIST care periods with agitation per mechanically ventilated patient
3. Number of DESIST care periods per patient with excessive sedation
4. Number of DESIST care periods with poor relaxation per mechanically ventilated patient
5. Number of DESIST care periods with poor ventilator synchronisation per mechanically ventilated patient

C. Adverse events

1. **Proportion of days during mechanical ventilation on which a sedation-related adverse event** (unplanned removal of NG tube, central line, arterial line, drain or peripheral line; unplanned extubation; staff injury; patient injury) occurred. Any combination of the listed adverse events will comprise an "adverse event day". The CRF included an "other" category, but these will not be included due to variation in reporting between centres.
2. **Proportion of patients receiving mechanical ventilation in whom a sedation-related adverse event occurred**

D. Sedative and Analgesic Drug Use
    1. Total use of intravenous sedative drugs per patient (propofol equivalents). Propofol was chosen as it is the most prevalent sedative drug.
    2. Proportion of ICU days on which ≥4000mg propofol or propofol equivalents were given. This is an index of likely deep sedation.
    3. Total use of intravenous analgesic drugs per patient (alfentanil equivalents). Alfentanil was chosen as it is the most prevalent analgesic drug.
    4. Proportion of patients receiving haloperidol

    The derivation of the conversions to propofol and alfentanil equivalents are described in appendix 3, together with the conversion chart for use in the analysis.

E. Duration of mechanical ventilation during index ICU admission (days)
F. Duration of ICU stay (days)
G. Duration of hospital stay (days)
H. ICU mortality
I. Hospital mortality

Exploratory outcomes

J. Patient experience and symptoms
    1. Intensive Care Experience questionnaire (ICE-Q) score for the following domains:
        i. Awareness of surroundings domain
        ii. Frightening experiences domain
        iii. Recall of experience domain
        iv. Satisfaction with care domain
        v. Responses to additional questions
    2. Impact of events scale revised (IES-R) score for the following
        i. Avoidance
        ii. Intrusion
        iii. Hyperarousal
        iv. Total score

Other outcomes

K. Nursing knowledge of sedation

Analysis of the outcomes listed in **bold type** will be included in the CSO (Chief Scientists Office; main funder) final report. Detailed algorithms for the derivation of the primary outcome and the sedation-related outcomes in section A. are provided in Appendix 1. A table indicating the conversion charts for drug doses used is shown in Appendix 3. Details for calculating scores for the Patient experience outcomes (J) are shown in Appendix 4.

Statistical Analysis

Characteristics of ICUs and patients

The following factors will be used to describe the ICUs in which the trial took place, and the patients included within each ICU (cluster)

ICU level
Number and proportion of eligible patients enrolled in each trial phase; occurrence of each sedation quality outcome in each trial phase

Patient level
Age, gender, APACHE II score, admission type, SICSAG ICU admission diagnosis

Comparisons of ICU level and patient level characteristics between ICUs

These variables will be used in the modelling to adjust for differences between ICUs and also changes within ICUs between the pre-intervention and post-implementation periods. Table 1a will describe the context for the trial at ICU and patient level, and describe the unadjusted data for each ICU during the pre-intervention and post-implementation periods. Table 1b will provide the same context measures summarised by the intervention group to which ICUs were randomised.

Process evaluation

We will record the compliance with the planned implementation strategy by the research group and local research implementation teams.

The process evaluation will capture data relevant to each of the three interventions as follows:

1. **"DESIST education".** We will record the proportion of ICU nursing staff who completed the DESIST education package and passed all modular assessments
2. **"DESIST process feedback".** We will record the number of process reports and slide sets provided to the ICUs. The maximum number of reports, including the implementation period report, will be six.
3. **"DESIST responsiveness monitoring".** We will record whether formal training in the use of the Responsiveness Index (RI) monitoring occurred according to a pre-specified training schedule. We will record the number of enrolled patients who received any period of RI monitoring. We will calculate the number of RI data logged by bedside nurses, based on the data recorded in the case record file.

The process evaluation will be presented as set out in table 2.

Qualitative analysis

Qualitative data were collected both during the pre-intervention and the implementation/post-implementation phases of the study. We conducted multi-professional focus groups in each ICU prior to the implementation phase to understand the current culture of sedation practice. During the implementation and post-implementation phases, participant observation took place at each ICU in three distinct timelines to understand the uptake of the interventions and changes in practice; end of implementation phase, midway in the post-implementation phase and at the end of the post-implementation phase. We also conducted multi-professional focus groups in the final month of the post-implementation phase, in which participants reflected on the uptake of the intervention(s) and

the changes of the sedation practice. Field notes from the final focus groups to summarise the main topics discussed were also taken.

Method

Data from field notes from participant observation and focus groups transcripts will be verbatim transcribed and then checked for accuracy of transcription by the qualitative researcher and by a member of the research team in each ICU. Data will be entered in NVivo 10 for windows software for qualitative analysis (QSR International, Ltd).

Data will be organised by ICU setting for coding. An inductive thematic analysis will be conducted without a pre-defined theoretical framework to allow the in-depth exploration and understanding of the impact of interventions on sedation management. Constant comparison will ensure that the thematic analysis represents all perspectives and negative cases will be sought. Validity checking of the coding will include recoding of data from 4 ICUs, representative of each intervention group, by an independent researcher. Discordant coding and agreement will be resolved by discussion within the wider research team. To build a valid argument for choosing the themes, the related literature will be searched to facilitate the interpretation of the data.

Coding:

1. Primary coding will involve identifying common patterns of experiences with each intervention in each ICU.
2. All data that relate to the already classified patterns will be explored to categorise engagers versus non-engagers; barriers and facilitators to adopting and implementing the intervention(s); Quality Improvement strategies used by each ICU; Changes in sedation practice.
3. Patterns of changes in sedation practice will be compared to the identified gaps in practice from the pre-intervention focus groups for each ICU. Related patterns will be combined and catalogued into sub-themes.
4. We will compare themes by characteristics of ICUs (i.e. size of ICU, patient case mix, staff levels).
5. We will compare themes by combination of interventions to identify any intervention(s) interaction patterns.

Comparison of ICUs in relation to engagement and adoption of the interventions will be summarised as below to support and inform the quantitative analysis.

1. Engagement and adoption with education package per ICU

Number of staff completing education package within 2 months	
Number of staff completing education package > 2months	
Number of staff revisiting education package	
Positive comments on education package	
Negative comments on education package	
Changes of sedation practice as a result of education package	Yes/No

2. Engagement and adoption with process feedback measures per ICU

Dissemination of process feedback measures	Yes/No

Strategies in place used to disseminate and adopt process measures	Yes/No
PDSA cycles generated	Yes/No
Positive comments on process measures	
Negative comments on process measures	
Changes of sedation practice as a result of process feedback measures	Yes/No

3. Engagement and adoption with responsiveness monitor per ICU

Positive attitude to the use of monitor	
Negative attitude to the use of monitor	
Changes of sedation practice as a result of the responsiveness monitor	Yes/No

4. Barriers and Facilitators to adopt and implement the intervention(s) per ICU – comparison across ICUs

ICU	Education package	Process feedback measures	Responsiveness monitor
1			
2			
3			
4			
5			
6			
7			
8			

5. Other initiatives that impacted on sedation management per ICU

ICU	Other initiatives
1	
2	
3	
4	
5	
6	
7	
8	

Primary outcome

Descriptive statistics

The percentage of DESIST care periods with optimum sedation will be summarised by ICU for the pre-intervention and post-implementation phases. (Table 3)

The percentage of DESIST care periods with optimum sedation will be summarised by randomised group (randomised to implement responsiveness technology Y/N; and randomised to implement process feedback Y/N) for the pre-intervention and post-implementation phases. (Table 4)

Multilevel model

The primary analysis will be a multilevel regression which uses outcome (pre-intervention or post-implementation) as the dependent variable; ICU, time period and ICU by time period interaction as the fixed effects independent variables at the ICU level; and age, sex and APACHE II score as the fixed effects independent variables at the admission level.

The primary outcome, occurrence of optimum sedation for each DESIST care period, is binary and therefore the dependent variable will follow a binomial distribution. Statistical models for such data are referred to as generalised linear mixed models.

A 3-level multilevel model will be fitted using MLWin, where DESIST care period is level 1, admission is level 2 and ICU is level 3. We fit a random intercept model, containing random variables for ICU and admission which are assumed to follow a normal distribution (Appendix 2A).

The multilevel model will not in the first instance make formal grouped comparisons between ICUs randomised / not randomised to **DESIST responsiveness monitoring (R)**; and between ICUs randomised / not randomised to **DESIST process feedback (P)**. Similarly, it will not make a formal grouped comparison between pre-intervention and post-implementation to assess the effect of **DESIST education (E)**. Instead, an odds ratio and 95% confidence interval will be calculated for the pre-intervention to post-implementation change within *each* ICU. An odds ratio value greater than one would indicate an increase in the proportion of DESIST care periods in which there was optimum sedation. Predicted values on the percentage scale will also be derived for the pre-intervention and post-implementation periods. (Table 5). Mean levels of age, sex and APACHE II score will be used to calculate the predicted values.

In the light of the observed variability in the odds ratio estimates across ICUs, and informed by the findings from the qualitative analysis described above, a decision will be made on whether it is appropriate to perform a pooled analysis across ICUs (Appendix 2B) to summarise intervention effects for any of E, R, P or the interaction between R and P. (Table 6)

Model checking

Parameter estimates may be non-robust to the failure of the assumed distribution of the random effects, therefore diagnostic checking of the residuals will be performed. Model-fitting problems will also occur if many individuals have almost all positive or all negative responses.

Parameter estimation

Different estimation methods are required when the response variable is binomial. Maximum likelihood estimation is computationally intensive and therefore quasi-likelihood methods are implemented in MLwiN. These will be used for model building, (for example, the addition of random slopes and interactions). MCMC (Markov Chain Monte Carlo) methods (the Metropolis-Hastings algorithm) will be used to estimate the coefficients from the final model as they will be less biased than those produced by IGLS (iterative generalised least squares) using quasi-likelihood. Estimates will be compared to their standard errors using an approximate Wald test.

Two intraclass correlations (ICC) will be calculated (Appendix 2C) for the multilevel model, one at each of level 2 (admission) and level 3 (ICU).

Alternative modelling strategy

In the event that computational difficulties prevent the successful fitting of the complex 3-level multilevel model described above, we will revert to an alternative strategy whereby a 2-level multilevel model will be fitted to each ICU separately, in which DESIST care period is level 1 and admission is level 2 (Appendix 2D). Time period will be included as an independent variable at ICU level; age, sex and APACHE II scores will be the independent variables at the admission level; and a random intercept for will be included for level 2 (admission).

Sensitivity analyses

We anticipate that implementation and uptake of the interventions will not be complete at the end of the 2 month implementation period, and is likely to continue during the post-intervention period. In addition, QI process is intended to continue throughout the post-intervention period through PDSA cycles and local initiatives stimulated by the intervention strategies. We will repeat the analysis including only post-implementation data recorded in the final 30 weeks of the study, which will assess the effect of the interventions after a 5-6 month total period of QI activity.

Secondary outcomes

Equations for the models to be used in the analysis of secondary outcomes are given in Appendix 2E.

Binary secondary outcomes (A1, A2, A3, A4; C1; D2) will be analysed in the same manner as the primary outcome.

Binary secondary outcomes measured at the patient or admission level (C2;H;I) will be analysed using a 2-level multilevel generalised linear model, including the same independent variables as used in the model for the primary outcome.

Continuous secondary outcomes (D1,D3) will be analysed using a 2-level multilevel normal linear model, including the same independent variables as used in the model for the primary outcome.

Secondary outcomes involving a count of a number of events (B1,B2,B3,B4,B5) will be analysed using a 2-level multilevel Poisson regression, including an offset term for the number of eligible care periods in an admission. The model will contain the same independent variables as used in the primary outcome model. A rate ratio and 95% confidence interval will be calculated for the pre-intervention to post-implementation change within each ICU. A rate ratio value greater than one would indicate an average increase in the outcome event count per admission.

Time-to-event secondary outcomes (E,F,G) will be analysed using a 2-level multilevel Cox proportional hazards regression model. The model will be fitted using a Poisson model in MLwiN by splitting follow-up time into as many intervals as there are events and will contain the same independent variables as used in the primary outcome analysis. Larger time intervals may be used if it becomes too computationally intensive which results in a close approximation to the Cox model.

The exploratory patient experience and symptoms outcomes (J1;J2) will be presented descriptively. Response rates (n,%) will be summarised by ICU. Median, lower and upper quartile values will be presented by ICU. If response rates are sufficiently high, and the amount and patterns of missing

data allow, analysis using a 2-level multilevel normal linear model will be considered. Although all elements of the ICE-Q and IES-R will be summarised, the main focus of the analysis for ICE-Q will be on the awareness of surroundings and frightening experiences domains. For IES-R the main focus will be on the total score. A description of the questionnaire elements, and how they are used to calculate domain scores, is shown in Appendix 4.

Completeness of nursing staff knowledge (K) score data will be summarised by time point (Implementation phase; Post-implementation phase) and ICU. Unadjusted data for the scores on the 10-point knowledge test for the Implementation and post-implementation phases will be summarised for the overall cohorts (and by individual ICU), and for the sub-set of nursing staff with complete paired tests undertaken before and after education. If considered feasible given the patterns of missing data, changes from Implementation to Post-implementation will be analysed using a 2-level (nurses within ICU) multilevel normal linear model, adjusting for the Implementation phase knowledge score. Further exploratory analysis will investigate graphically, at nurse and ICU level, the association between the timing of undertaking the education package and the Implementation phase knowledge score.

Validation

The main analysis of the primary outcome and the derivation of the primary and key secondary outcomes will be verified by a second statistician.

Description of changes from protocol Statistical Methods section

The main developments in this statistical analysis plan from the statistical methods outlined in the trial protocol are as follows:

1. The effect of **DESIST education** will now be estimated within the same multilevel model used to assess the effects of **DESIST process feedback** and **DESIST responsiveness monitoring**, using data from all eight participating ICU sites. This will enable a more generalizable and more precise estimation of the DESIST education effect.
2. The main multilevel model will now be a 3-level model analysing binary outcomes at the DESIST care period level in a multilevel logistic regression. This differs from the protocol specified analysis which would have been a 2-level multilevel normal linear model with data aggregated at the admission level. The 3-level model will more appropriately reflect the underlying structure of the study data and will avoid the requirement for the sensitivity analysis weighted by length of stay.
3. Patients admitted with a diagnosis of status epilepticus will be excluded from all analyses.
4. Ventilation days occurring during readmissions to ICU will not be included when calculating duration of mechanical ventilation in ICU. Only the index ICU admission will be considered.

5. The analysis of the education data, in relation to nursing knowledge before and after the implementation of the education package, is included in the main analysis plan.
6. An exploratory analysis of patient responses to the ICE-Q patient experience questionnaire, and the IER-R questionnaire is included.

Example tables

Table 1a: Admissions enrolled, DESIST care periods included in analysis of primary outcome, and characteristics of admissions by ICU and trial phase

		Intensive care unit							
	Phase	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Percentage of eligible admissions enrolled	Pre-intervention								
	Post-implementation								
Number of admissions enrolled	Pre-intervention								
	Post-implementation								
Percentage of eligible DESIST care periods with data for primary outcome	Pre-intervention								
	Post-implementation								
Number of DESIST care periods with data for primary outcome	Pre-intervention								
	Post-implementation								
Mean (SD) for age (years)	Pre-intervention								
	Post-implementation								
Percentage male	Pre-intervention								
	Post-implementation								
Mean (SD) for APACHE II score	Pre-intervention								
	Post-implementation								
Percentage with each admission type									
type one	Pre-intervention								
	Post-implementation								
…	Pre-intervention								
	Post-implementation								
Percentage in SICSAG ICU admission diagnostic grouping									
category one	Pre-intervention								
	Post-implementation								
…	Pre-intervention								
	Post-implementation								

Table 1b: Admissions enrolled, DESIST care periods included in analysis of primary outcome, and characteristics of admissions by intervention and trial phase

		Responsiveness technology		**Process feedback**	
	Phase	**Implemented**	**Not implemented**	**Implemented**	**Not implemented**
Percentage of eligible admissions enrolled	Pre-intervention				
	Post-implementation				
Number of admissions enrolled	Pre-intervention				
	Post-implementation				
Percentage of eligible DESIST care periods with data for primary outcome	Pre-intervention				
	Post-implementation				
Number of DESIST care periods with data for primary outcome	Pre-intervention				
	Post-implementation				
Mean (SD) for age (years)	Pre-intervention				
	Post-implementation				
Percentage male	Pre-intervention				
	Post-implementation				
Mean (SD) for APACHE II score	Pre-intervention				
	Post-implementation				
Percentage with each admission type					
type one	Pre-intervention				
	Post-implementation				
…	Pre-intervention				
	Post-implementation				
Percentage in SICSAG ICU admission diagnostic grouping					
category one	Pre-intervention				
	Post-implementation				
…	Pre-intervention				
	Post-implementation				

Table 2: Description of the key elements of the processes evaluated in the trial. (a) description of the key elements of implementation of each of the three interventions; (b) description of the implementation and post-implementation follow up and fieldwork visits undertaken for all ICUs.

ICU	DESIST Education			DESIST Process feedback				DESIST responsiveness monitoring			
	Proportion of staff completing training	Proportion of staff revisiting education package online	Proportion of staff completing pre- and post-test	Number of process reports provided during intervention period	Staff involved in disseminating process reports	Means of dissemination of process reports from study team to site team and within site team	Number/ Type of improvement initiatives generated as a result of process reports	Training visits completed	Number of staff trained	Proportion of patients receiving any monitoring	Number of RI values logged per patient
1											
2											
3											
4											
etc											

Baseline Focus Groups – identify current gaps/ barriers in practice	Implementation strategy			Intervention phase					Post-intervention Focus Group - reflection
	Implementation pack developed	Implementation visit	Teleconference/ meeting 1 month post implementation visit	1st visit- fieldwork Start of intervention	2nd visit fieldwork Mid-intervention	3rd visit fieldwork End-intervention	Mid-intervention stakeholders meeting	Post-intervention stakeholders meeting/ teleconference	

Table 3a: Descriptive statistics for primary outcome and sedation quality outcomes by ICU and trial phase

		Intensive care unit							
Primary outcome	**Phase**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Percentage of DESIST care periods with optimum sedation	Pre-intervention								
	Post-implementation								
Sedation Quality Components									
Percentage of DESIST care periods with excessive sedation	Pre-intervention								
	Post-implementation								
Percentage of DESIST care periods with patient agitation	Pre-intervention								
	Post-implementation								
Percentage of DESIST care periods with poor relaxation	Pre-intervention								
	Post-implementation								
Percentage of DESIST care periods with poor ventilator synchronisation	Pre-intervention								
	Post-implementation								

Table 3b: Descriptive statistics for patient-level sedation outcomes by ICU and trial phase

		Intensive Care Unit							
Patient-level sedation outcomes	**Phase**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Mean number of DESIST care periods per admission with optimum sedation	Pre-intervention								
	Post-implementation								
Mean number of DESIST care periods per admission with excessive sedation	Pre-intervention								
	Post-implementation								
Mean number of DESIST care periods per admission with patient agitation	Pre-intervention								
	Post-implementation								
Mean number of DESIST care periods per admission with poor relaxation	Pre-intervention								
	Post-implementation								
Mean number of DESIST care periods per admission with poor ventilator synchronisation	Pre-intervention								
	Post-implementation								

Table 3c: Descriptive statistics for adverse events and sedative and analgesic drug use outcomes by ICU and trial phase

		Intensive Care Unit							
Adverse Events	**Phase**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Percentage of ICU days on which sedation-related adverse event(s) occurred	Pre-intervention								
	Post-implementation								
Percentage of admissions during which sedation-related adverse event(s) occurred	Pre-intervention								
	Post-implementation								
Sedative and Analgesic Drug Use									
Mean use of intravenous sedative drugs per admission (propofol equivalents)	Pre-intervention								
	Post-implementation								
Percentage of ICU days on which ≥4000mg propofol or propofol equivalents given	Pre-intervention								
	Post-implementation								
Mean use of intravenous analgesic drugs per admission (morphine equivalents)	Pre-intervention								
	Post-implementation								

Table 3d: Descriptive statistics for time-to-event and mortality outcomes by ICU and trial phase

		Intensive Care Unit							
Outcomes	**Phase**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Median duration of mechanical ventilation during ICU stay (days)	Pre-intervention								
	Post-implementation								
Median duration of ICU stay (days)	Pre-intervention								
	Post-implementation								
Median duration of hospital stay (days)	Pre-intervention								
	Post-implementation								
ICU mortality	Pre-intervention								
	Post-implementation								
Hospital mortality	Pre-intervention								
	Post-implementation								

Table 3e: Descriptive statistics for exploratory outcomes by ICU and trial phase

Patient experience and symptom measures	Phase	Intensive Care Unit							
		1	2	3	4	5	6	7	8

Table 4a: Descriptive statistics for primary outcome and sedation quality component outcomes by intervention and trial phase

Primary outcome	Phase	Responsiveness technology		Process feedback	
		Implemented	Not implemented	Implemented	Not implemented
Proportion of DESIST care periods with optimum sedation	Pre-intervention				
	Post-implementation				
Sedation Quality Components					
Proportion of DESIST care periods with excessive sedation	Pre-intervention				
	Post-implementation				
Proportion of DESIST care periods with patient agitation	Pre-intervention				
	Post-implementation				
Proportion of DESIST care periods with poor relaxation	Pre-intervention				
	Post-implementation				
Proportion of DESIST care periods with poor ventilator synchronisation	Pre-intervention				
	Post-implementation				

Table 4b: Descriptive statistics for patient-level sedation outcomes by intervention and trial phase

Patient-Level Sedation Outcomes	Phase	Responsiveness technology		Process feedback	
		Implemented	Not implemented	Implemented	Not implemented
Mean number of DESIST care periods per admission with optimum sedation	Pre-intervention				
	Post-implementation				
Mean number of DESIST care periods per admission with excessive sedation	Pre-intervention				
	Post-implementation				
Mean number of DESIST care periods per admission with patient agitation	Pre-intervention				
	Post-implementation				
Mean number of DESIST care periods per admission with poor relaxation	Pre-intervention				
	Post-implementation				
Mean number of DESIST care periods per admission with poor ventilator synchronisation	Pre-intervention				
	Post-implementation				

Table 4c: Descriptive statistics for adverse events and sedative and analgesic drug use outcomes by intervention and trial phase

		Responsiveness technology		Process feedback	
Adverse Events	**Phase**	**Implemented**	**Not implemented**	**Implemented**	**Not implemented**
Percentage of ICU days on which sedation-related adverse event(s) occurred	Pre-intervention				
	Post-implementation				
Percentage of admissions during which sedation-related adverse event(s) occurred	Pre-intervention				
	Post-implementation				
Sedative and Analgesic Drug Use					
Mean use of intravenous sedative drugs per admission (propofol equivalents)	Pre-intervention				
	Post-implementation				
Percentage of ICU days on which ≥4000mg propofol or propofol equivalents given	Pre-intervention				
	Post-implementation				
Mean use of intravenous analgesic drugs per admission (morphine equivalents)	Pre-intervention				
	Post-implementation				

Table 4d: Descriptive statistics for time-to-event and mortality outcomes by intervention and trial phase

		Responsiveness technology		Process feedback	
Outcomes	**Phase**	**Implemented**	**Not implemented**	**Implemented**	**Not implemented**
Median duration of mechanical ventilation during ICU stay (days)	Pre-intervention				
	Post-implementation				
Median duration of ICU stay (days)	Pre-intervention				
	Post-implementation				
Median duration of hospital stay (days)	Pre-intervention				
	Post-implementation				
ICU mortality	Pre-intervention				
	Post-implementation				
Hospital mortality	Pre-intervention				
	Post-implementation				

Table 4e: Descriptive statistics for exploratory outcomes by intervention and trial phase

Patient experience and symptom measures	Phase	Responsiveness technology		Process feedback	
		Implemented	Not implemented	Implemented	Not implemented

Table 5a: Results from modelling of primary outcome and sedation quality component outcomes by ICU and trial phase

Primary outcome	**Phase**	**Intensive care unit**							
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Predicted percentage of DESIST care periods with optimum sedation	Pre-intervention								
	Post-implementation								
	Odds Ratio (95% CI)								
Sedation Quality Components									
Predicted percentage of DESIST care periods with excessive sedation	Pre-intervention								
	Post-implementation								
	Odds Ratio (95% CI)								
Predicted percentage of DESIST care periods with patient agitation	Pre-intervention								
	Post-implementation								
	Odds Ratio (95% CI)								
Predicted percentage of DESIST care periods with poor relaxation	Pre-intervention								
	Post-implementation								
	Odds Ratio (95% CI)								
Predicted percentage of DESIST care periods with poor ventilator synchronisation	Pre-intervention								
	Post-implementation								
	Odds Ratio (95% CI)								

Table 5b: Results from modelling of patient-level sedation outcomes by ICU and trial phase

Patient-Level Sedation Outcomes	Phase	Intensive Care Unit							
		1	2	3	4	5	6	7	8
Predicted mean number of DESIST care periods per admission with optimum sedation	Pre-intervention								
	Post-implementation								
	Rate Ratio (95% CI)								
Predicted mean number of DESIST care periods per admission with excessive sedation	Pre-intervention								
	Post-implementation								
	Rate Ratio (95% CI)								
Predicted mean number of DESIST care periods per admission with patient agitation	Pre-intervention								
	Post-implementation								
	Rate Ratio (95% CI)								
Predicted mean number of DESIST care periods per admission with poor relaxation	Pre-intervention								
	Post-implementation								
	Rate Ratio (95% CI)								
Predicted mean number of DESIST care periods per admission with poor ventilator synchronisation	Pre-intervention								
	Post-implementation								
	Rate Ratio (95% CI)								

Table 5c: Results from modelling of adverse events and sedative and analgesic drug use outcomes by ICU and trial phase

		Intensive Care Unit							
Adverse Events	**Phase**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Predicted percentage of ICU days on which sedation-related adverse event(s) occurred	Pre-intervention								
	Post-implementation								
	Odds Ratio (95% CI)								
Predicted percentage of admissions during which sedation-related adverse event(s) occurred	Pre-intervention								
	Post-implementation								
	Odds Ratio (95% CI)								
Sedative and Analgesic Drug Use									
Predicted mean use of intravenous sedative drugs per admission (propofol equivalents)	Pre-intervention								
	Post-implementation								
	Difference (95% CI)								
Predicted percentage of ICU days on which ≥4000mg propofol or propofol equivalents given	Pre-intervention								
	Post-implementation								
	Odds Ratio (95% CI)								
Predicted mean use of intravenous analgesic drugs per admission (morphine equivalents)	Pre-intervention								
	Post-implementation								
	Difference (95% CI)								

Table 5d: Results from modelling of time-to-event and mortality outcomes by ICU and trial phase

Outcome	Phase	Intensive Care Unit							
		1	2	3	4	5	6	7	8
Predicted median duration of mechanical ventilation during ICU stay (days)	Pre-intervention								
	Post-implementation								
	Hazard Ratio (95% CI)								
Predicted median duration of ICU stay (days)	Pre-intervention								
	Post-implementation								
	Hazard Ratio (95% CI)								
Predicted median duration of hospital stay (days)	Pre-intervention								
	Post-implementation								
	Hazard Ratio (95% CI)								
Predicted ICU mortality	Pre-intervention								
	Post-implementation								
	Odds Ratio (95% CI)								
Predicted hospital mortality	Pre-intervention								
	Post-implementation								
	Odds Ratio (95% CI)								

Table 5e: Results from modelling of exploratory outcomes by ICU and trial phase

Patient experience and symptom measures	Phase	Intensive Care Unit							
		1	2	3	4	5	6	7	8

Table 6a: Results from modelling of primary and sedation quality component outcomes by intervention and trial phase

Primary outcome	Phase	Responsiveness technology		Process feedback	
		Implemented	Not implemented	Implemented	Not implemented
Predicted percentage of DESIST care periods with optimum sedation	Pre-intervention				
	Post-implementation				
	Odds Ratio (95% CI)				
Sedation Quality Components					
Predicted percentage of DESIST care periods with excessive sedation	Pre-intervention				
	Post-implementation				
	Odds Ratio (95% CI)				
Predicted percentage of DESIST care periods with patient agitation	Pre-intervention				
	Post-implementation				
	Odds Ratio (95% CI)				
Predicted percentage of DESIST care periods with poor relaxation	Pre-intervention				
	Post-implementation				
	Odds Ratio (95% CI)				
Predicted percentage of DESIST care periods with poor ventilator synchronisation	Pre-intervention				
	Post-implementation				
	Odds Ratio (95% CI)				

Note. Table headings will differ slightly if significant responsiveness monitoring * process feedback interaction is found.

Table 6b: Results from modelling of patient-level sedation outcomes by intervention and trial phase

Patient-Level Sedation Outcomes	**Phase**	**Responsiveness technology**		**Process feedback**	
		Implemented	**Not implemented**	**Implemented**	**Not implemented**
Predicted mean number of DESIST care periods per admission with optimum sedation	Pre-intervention				
	Post-implementation				
	Rate Ratio (95% CI)				
Predicted mean number of DESIST care periods per admission with excessive sedation	Pre-intervention				
	Post-implementation				
	Rate Ratio (95% CI)				
Predicted mean number of DESIST care periods per admission with patient agitation	Pre-intervention				
	Post-implementation				
	Rate Ratio (95% CI)				
Predicted mean number of DESIST care periods per admission with poor relaxation	Pre-intervention				
	Post-implementation				
	Rate Ratio (95% CI)				
Predicted mean number of DESIST care periods per admission with poor ventilator synchronisation	Pre-intervention				
	Post-implementation				
	Rate Ratio (95% CI)				

Table 6c: Results from modelling of adverse events and sedative and analgesic drug use outcomes by intervention and trial phase

Adverse Events	**Phase**	**Responsiveness technology**		**Process feedback**	
		Implemented	**Not implemented**	**Implemented**	**Not implemented**
Predicted percentage of ICU days on which sedation-related adverse event(s) occurred	Pre-intervention				
	Post-implementation				
	Odds Ratio (95% CI)				
Predicted percentage of admissions during which sedation-related adverse event(s) occurred	Pre-intervention				
	Post-implementation				
	Odds Ratio (95% CI)				
Sedative and Analgesic Drug Use					
Predicted mean use of intravenous sedative drugs per admission (propofol equivalents)	Pre-intervention				
	Post-implementation				
	Difference (95% CI)				
Predicted percentage of ICU days on which ≥4000mg propofol or propofol equivalents given	Pre-intervention				
	Post-implementation				
	Odds Ratio (95% CI)				
Predicted mean use of intravenous analgesic drugs per admission (morphine equivalents)	Pre-intervention				
	Post-implementation				
	Difference (95% CI)				

Table 6d: Results from modelling of time-to-event and mortality outcomes by intervention and trial phase

Outcome	**Phase**	**Responsiveness technology**		**Process feedback**	
		Implemented	**Not implemented**	**Implemented**	**Not implemented**
Predicted median duration of mechanical ventilation during ICU stay (days)	Pre-intervention				
	Post-implementation				
	Hazard Ratio (95% CI)				
Predicted median duration of ICU stay (days)	Pre-intervention				
	Post-implementation				
	Hazard Ratio (95% CI)				
Predicted median duration of hospital stay (days)	Pre-intervention				
	Post-implementation				
	Hazard Ratio (95% CI)				
Predicted ICU mortality	Pre-intervention				
	Post-implementation				
	Odds Ratio (95% CI)				
Predicted hospital mortality	Pre-intervention				
	Post-implementation				
	Odds Ratio (95% CI)				

Table 6e: Results from modelling of exploratory outcomes by intervention and trial phase

Patient experience and symptom measures	**Phase**	**Responsiveness technology**		**Process feedback**	
		Implemented	**Not implemented**	**Implemented**	**Not implemented**

Appendix 1 Sedation-related outcomes

The five outcome measures which are based on SQAT are derived using all the 12 hour periods of care (DESIST care periods) for which a SQAT form has been submitted and patient had received mechanical ventilation, was NOT receiving neuromuscular paralysis, and data are available from required SQAT Sections.

Derive for each specified time period the number of DESIST care periods for which:
(a) SQAT form was expected to be completed,
(b) SQAT form was NOT submitted,
(c) SQAT form was submitted but incomplete data for Sections 2 or 5,
(d) SQAT form was submitted with complete data for Sections 2 and 5 but patient had NOT received mechanical ventilation or was receiving neuromuscular paralysis,
(e) SQAT form was submitted with complete data for Sections 2 and 5, and patient had received mechanical ventilation, was NOT receiving neuromuscular paralysis, but incomplete data for Sections 3, 4, 6b, 6c, 7, 8a or 9

Proportion of DESIST care periods with excessive sedation
The number of DESIST care periods where patient received sedative and/or analgesic drug, had NOT received advanced ventilator modes or therapeutic hypothermia, does NOT have record of raised intracranial pressure or cerebral oedema, and current sedation/agitation recorded as "My patient does not respond to their name being called but movement is observed in response to physical stimulation" ***or*** "My patient shows no response to physical stimulation", as a proportion of those DESIST care periods for mechanically ventilated patients NOT receiving neuromuscular paralysis with complete data for required SQAT Sections.

Denominator derived by counting number of DESIST care periods where:
Section 2 (received mechanical ventilation) = "Yes", ***and***
Section 5 (currently receiving neuromuscular paralysis) = "No", ***and***
Sections 3, 4, 7 and 9 all completed

Numerator derived by counting number of those DESIST care periods in the denominator where:
Section 3 (received sedative) = "Yes" ***and/or*** Section 4 = (received analgesic drug) = "Yes", ***and***
Section 9 (received advanced ventilator modes and/or therapeutic hypothermia) = "No", ***and***
Raised Intracranial Pressure question on the Daily Case Report = "No" ***or*** no response, ***and***
Cerebral Oedema question on the Daily Case Report = "No" ***or*** no response, ***and***
Section 7 (current sedation/agitation) = "My patient does not respond to their name being called but movement is observed in response to physical stimulation" ***or*** "My patient shows no response to physical stimulation"

Proportion of DESIST care periods with patient agitation

The number of DESIST care periods where current sedation/agitation recorded as “On observation patient is currently combative or violent or dangerous/aggressive towards staff or pulling/removing tubes, catheters or drains” or agitated behaviour recorded as “Yes”, as a proportion of those DESIST care periods for mechanically ventilated patients NOT receiving neuromuscular paralysis with complete data for required SQAT Sections.

Denominator derived by counting number of DESIST care periods where:
Section 2 (received mechanical ventilation) = "Yes"", ***and***
Section 5 (receiving neuromuscular paralysis) = "No", ***and***
Sections 7 and 8a both completed

Numerator derived by counting number of those DESIST care periods in the denominator where:
Section 7 (current sedation/agitation) = "On observation patient is currently combative or violent or dangerous/aggressive towards staff or pulling/removing tubes, catheters or drains", ***and/or***
Section 8a (agitated behaviour) = "Yes"

Proportion of DESIST care periods with poor relaxation

The number of DESIST care periods where limb movement recorded as “difficult to move most of the time” ***or*** “actively resisting movement most of the time”, as a proportion of those DESIST care periods for mechanically ventilated patients NOT receiving neuromuscular paralysis with complete data for required SQAT Sections.

Denominator derived by counting number of DESIST care periods where:
Section 2 (received mechanical ventilation) = "Yes", ***and***
Section 5 (receiving neuromuscular paralysis) = "No", ***and***
Section 6b completed

Numerator derived by counting number of those DESIST care periods in the denominator where:
Section 6b (limb movement) = “difficult to move most of the time” ***or*** “actively resisting movement most of the time”

Proportion of DESIST care periods with poor ventilator synchronisation

The number of DESIST care periods where compliance with ventilator recorded as “tolerating ventilation but coughing/gagging frequently” ***or*** “unable to control ventilation due to poor patient synchronisation despite different modes tested”, as a proportion of those DESIST care periods for mechanically ventilated patients NOT receiving neuromuscular paralysis with complete data for required SQAT Sections.

Denominator derived by counting number of DESIST care periods where:
Section 2 (receiving mechanical ventilation) = "Yes", ***and***
Section 5 (receiving neuromuscular paralysis) = "No", ***and***
Section 6c completed

Numerator derived by counting number of those DESIST care periods in the denominator where:
Section 6c (compliance with ventilator) = “tolerating ventilation but coughing/gagging frequently” ***or*** “unable to control ventilation due to poor patient synchronisation despite different modes tested”

Proportion of DESIST care periods with optimum sedation

The number of DESIST care periods where none out of excessive sedation, agitation, poor relaxation, and poor ventilation synchronisation were present, as a proportion of those DESIST care periods for mechanically ventilated patients NOT receiving neuromuscular paralysis with complete data for required SQAT Sections.

Denominator derived by counting number of DESIST care periods where:
Section 2 (received mechanical ventilation) = "Yes", ***and***
Section 5 (receiving neuromuscular paralysis) = "No", ***and***
Sections 3, 4, 6b, 6c, 7, 8a and 9 all completed

Numerator derived by counting number of those DESIST care periods in the denominator where:
Excessive sedation ≠ "Yes", ***and***
Agitation ≠ "Yes", ***and***
Poor relaxation ≠ "Yes", ***and***
Poor ventilator synchronisation ≠ "Yes"

Excessive sedation = "Yes" defined as:
Section 3 (received sedative) = "Yes" ***and/or*** Section 4 = (received analgesic drug) = "Yes", ***and***
Section 9 (received advanced ventilator modes and/or therapeutic hypothermia) = "No", ***and***
Raised Intracranial Pressure question on the Daily Case Report = "No" ***or*** no response, ***and***
Cerebral Oedema question on the Daily Case Report = "No" ***or*** no response, ***and***
Section 7 (current sedation/agitation) = "My patient does not respond to their name being called but movement is observed in response to physical stimulation" ***or*** "My patient shows no response to physical stimulation"

Agitation = "Yes" defined as:
Section 7 (current sedation/agitation) = "On observation patient is currently combative or violent or dangerous/aggressive towards staff or pulling/removing tubes, catheters or drains", ***and/or***
Section 8a (agitated behaviour) = "Yes"

Poor relaxation = "Yes" defined as:
Section 6b (limb movement) = “difficult to move most of the time” ***or*** “actively resisting movement most of the time”

Poor ventilator synchronisation = "Yes" defined as:
Section 6c (compliance with ventilator) = “tolerating ventilation but coughing/gagging frequently” ***or*** “unable to control ventilation due to poor patient synchronisation despite different modes tested”

Appendix 2 Primary and secondary outcome modelling

A: 3-level random intercepts model with fixed effects for the ICUs.

$$y_{ijk} \sim Binomial(1, \pi_{ijk})$$

$$\log it(\pi_{ijk}) = \beta_0 + u_{jk} + v_k + \beta_1 ICU + \beta_2 PHASE + \beta_3 ICU * PHASE + \beta_4 AGE + \beta_5 SEX + \beta_6 APACHE$$

Where $u_{jk} \sim N(0, \sigma_u^2)$, $v_k \sim N(0, \sigma_v^2)$ and β_1 and β_3 represent 7 estimated coefficients for the ICUs. In this formulation *i,j* and *k* index the level 1 (DESIST care period),2 (admission) and 3 (ICU) units respectively.

B: 3-level random intercepts model for the interventions and an interaction; Responsive Monitoring (R) and Process Feedback (P).

$$y_{ijk} \sim Binomial(1, \pi_{ijk})$$

$$\log it(\pi_{ijk}) = \beta_0 + u_{jk} + v_k + \beta_1 TRT\_R + \beta_2 TRT\_P + \beta_3 PHASE + \beta_4 TRT\_R * PHASE + \beta_5 TRT\_P * PHASE + \beta_6 TRT\_R * TRT\_P + \beta_7 TRT\_R * TRT\_P * PHASE + \beta_7 AGE + \beta_8 SEX + \beta_9 APACHE$$

Where $u_{jk} \sim N(0, \sigma_u^2)$ and $v_k \sim N(0, \sigma_v^2)$.

In the absence of a significant R*P interaction, the effect of R will be assessed using the log-odds ratio β_4. Similarly the effect of P will be assessed using the log-odds ratio β_5. Finally, Education would be assessed based on the log-odds ratio β_3.

C: Intraclass correlations

Two intraclass correlations (ICC) will be calculated for the 3-level model. The first is the level-3 ICC at the ICU level, the correlation between DESIST care periods in the same ICU:

$$\rho = \frac{\sigma_v^2}{\sigma_v^2 + \sigma_u^2 + \frac{\pi^2}{3}} \quad .$$

The second is the level-2 ICC at the admissions-within-ICU level, the correlation between DESIST care periods in the same admission and ICU:

$$\rho = \frac{\sigma_v^2 + \sigma_u^2}{\sigma_v^2 + \sigma_u^2 + \frac{\pi^2}{3}} \quad .$$

D: 2-level random intercept model fitted separately to each ICU.

$$y_{ij} \sim Binomial(1, \pi_{ij})$$

$$\log it(\pi_{ij}) = \beta_0 + u_j + \beta_1 PHASE + \beta_2 AGE + \beta_3 SEX + \beta_4 APACHE$$

Where $u_j \sim N(0, \sigma_u^2)$. In this formulation *i* and *j* index the level 1 (DESIST care period) and level 2 (admission) unit respectively.

E: Secondary Outcomes.

Binary secondary outcomes measured at the patient or admission level:

$$y_{ij} \sim Binomial(1, \pi_{ij})$$

$$\log it(\pi_{ij}) = \beta_0 + u_j + \beta_1 ICU + \beta_2 PHASE + \beta_3 ICU * PHASE + \beta_4 AGE + \beta_5 SEX + \beta_6 APACHE$$

Where $u_j \sim N(0, \sigma_u^2)$ and β_1 and β_3 represent 7 estimated coefficients for the ICUs. In this formulation *i* and *j* index the level 1 (admission) and level 2 (ICU) unit respectively.

Continuous secondary outcomes:

$$y_{ij} \sim N(XB, \Omega)$$

$$y_{ij} = \beta_0 + u_j + e_{ij} + \beta_1 ICU + \beta_2 PHASE + \beta_3 ICU * PHASE + \beta_4 AGE + \beta_5 SEX + \beta_6 APACHE$$

Where $u_j \sim N(0, \sigma_u^2)$, $e_{ij} \sim N(0, \sigma_e^2)$ and β_1 and β_3 represent 7 estimated coefficients for the ICUs. In this formulation *i* and *j* index the level 1 (admission) and level 2 (ICU) unit respectively.

Secondary outcomes involving a count of a number of events:

$$y_{ij} \sim Poisson(\pi_{ij})$$

$$\log(\pi_{ij}) = \beta_0 + u_j + \beta_1 ICU + \beta_2 PHASE + \beta_3 ICU * PHASE + \beta_4 AGE + \beta_5 SEX + \beta_6 APACHE + \ln(Number\ of\ Desist\ Care\ Periods)$$

Where $u_j \sim N(0, \sigma_u^2)$.

Time-to-event secondary outcomes:

Will be fitted using a Poisson model with a log link as above, where the hazard rate is assumed constant within the observed time intervals. If there are tied observations at any time interval, the logarithm of the number of failures will be treated as an offset in the model.

Appendix 3 Derivation of conversion to propofol and alfentanil equivalents for use in the analysis

Drug classification

Only drugs administered intravenously will be included in this analysis. Drugs were recorded on each day on the CRF; a range of pre-specified sedative and analgesic drugs were included, with the total daily dose recorded. In addition, "other" drugs could be recorded according to the discretion of the local research teams. The CRFs for each site were individualised when appropriate in order to capture the commonly used drugs, and drug infusion concentrations. Drug conversion charts to assist conversion from total volume of given drug solution concentrations to total daily doses were also provided.

The actual reported drugs used were viewed across all ICUs after the majority of data entry was completed. Based on prevalence of use, the index drug was chosen as **propofol** (sedative) and **alfentanil** (analgesic). These drugs accounted for the majority of sedation and analgesis recorded in all ICUs. The drugs included in the assessment of total sedative and analgesic use were as follows, based on frequency of use across and within ICUs and intravenous route of administration:

Sedative drugs: propofol, midazolam, dexmedetomidine

Analgesic drugs: alfentanil, fentanyl, morphine, remifentanil

Antipsychotic medications: haloperidol (usually intermittent doses)

The research group recognised the possible importance of methadone administered enterally, if this were a prevalent drug in some ICU populations. A search of the recorded drug administration data from the database indicated only 50 patients in total received methadone during ICU stay. Given the uncertainties in drug conversion for this drug, and its relative rarity, a decision to ignore methadone was made.

Drug equivalence

In order to describe and compare intravenous sedative and analgesic use per patient in the analysis, a conversion to an index drug is needed. Propofol and alfentanil were the standard drugs used in all ICUs, and were chosen as reference. Given the different potencies and pharmacokinetics of each drug, the conversion is not straightforward. To inform this conversion a search of published literature was undertaken, in collaboration with the pharmacy department at Edinburgh Royal Infirmary and drug information service. This was used to justify the conversion used.

Midazolam to propofol: A conversion factor of 1mg midazolam to 10mg propofol is supported by the literature in terms of equipotency for sedation and analgesia. Rates of clearance for midazolam are slightly longer than propofol, and some evidence suggests accumulation in patients with hepatic and renal failure. **A ratio of 0.1mg midazolam: 1mg propofol was used.**

Dexmedetomidine to propofol: As dexmedetomidine is a relatively newly licensed drug for longer term infusion, especially in Europe, there is relatively little experience to inform clinical equivalence

with propofol. The half-life of dexmedetomidine is also longer than propofol and infusion rates are currently recommended to be changed hourly. The best method for deriving equivalence was thought to be the PRODEX study[1], in which a similar RASS sedation score was targeted with each agent, and data are available for the mean doses utilised in each group. Median (IQR) doses were 0.925 (0.673 to 1.170) µg/kg/h versus 1.752 (1.211 to 2.424) mg/kg/h for dexmedetomidine and propofol respectively. The RASS scores were slightly higher in the dexmedetomidine group, but this difference was clinically small (dexmedetomidine −1.0 (−1.9 to −0.2); propofol −1.7 (−2.5 to −0.7)) and it was decided not to adjust for this variation. **A ratio of 0.53µg dexmedetomidine: 1mg propofol was used.**

Fentanyl to alfentanil: The analgesic potency of alfentanil is stated to be 25% that of fentanyl, but the duration of action of alfentanil is also 30-35% of fentanyl.[2] Although the onset of action of alfentanil is four times more rapid than that of an equianalgesic dose of fentanyl this was not considered relevant to equivalent dosage by continuous infusion for sedation. Given the shorter duration of action of alfentanil the pragmatic decision was made to treble the equivalent dose. This resulted in an equivalent dose of 1mg alfentanil having similar potency to 0.25mg fentanyl; to make an adjustment for the longer duration of duration of fentanyl we reduced the fentanyl dose further to 33% of the equipotent dose. **A ratio of 0.08mg (fentanyl): 1mg alfentanil was used**

Morphine to alfentanil: Intravenous alfentanil is 15 times more potent that IV morphine.[3,4] This would equate to an equipotent equivalent of 1mg of alfentanil being roughly equivalent to 15mg morphine. However, the duration of action of alfentanil is significantly shorter than morphine after bolus injection (15 minutes versus 2-3 hours). In addition, the clearance of alfentanil is minimally affected by organ dysfunction, but morphine elimination is significantly affected by renal dysfunction (through active metabolites), and may be affected by significant hepatic dysfunction. However, in clinical practice morphine use is generally avoided in patients with renal dysfunction, and/or hepatic failure. An equivalent dose therefore, can only be estimated. Based on the relative potencies, and difference in duration of action of 6-8 times longer for morphine, we estimated that the dose of alfentanil by infusion would be approximately 6 times greater due to shorter duration of action. **A ratio of 2.5mg morphine: 1mg alfentanil was used.**

Remifentanil to alfentanil: The equivalent doses of alfentanil and remifentanil are not established. The relationship is complex due to differing potencies, but especially very different pharmacokinetics. Remifentanil is cleared predictably by plasma esterases and has a very short half-life. Publications have suggested that remifentanil is either equipotent to fentanyl[5,6], up to twice as potent[7], or potentially >15 times more potent.[8] As the alfentanil SPC indicates that fentanyl is 4 times more potent than alfentanil, this suggests that 4-8µg alfentanil would be roughly equivalent to 1µg remifentanil. However, remifentanil has a very short duration of action and when used in practice, mainly in anaesthesia, the alfentanil to remifentanil dose ratio can vary from 30:1 to 10:1 for induction doses and from 10:1 to 1:1 for maintenance infusions. A meta-analysis of studies of remifentanil use for sedation in the ICU described available studies to 2009.[8] One study compared remifentanil 9-12 µg/kg/h with morphine 40-60 µg/kg/h. Using an extrapolation with alfentanil 15 times more potent than morphine would suggest that 3µg remifentanil is approximately equivalent to 1µg alfentanil. The ratio, in opposite direction to direct comparisons of potency, may reflect the different pharmacokinetics of the drugs, or non-titration to equivalent clinical end-points. A more recent small trial comparing midazolam/fentanyl with propofol/remifentanil based sedation during

therapeutic hypothermia after cardiac arrest targeted a similar clinical motor sedation score. The actual mean analgesic doses during infusion were 630µg/hr for remifentanil, and 200µg/hr fentanyl (ratio 3:1). This study is not directly comparable to the patient in DESIST as all had possible brain injury, different sedatives were used, and therapeutic hypothermia could alter pharmacokinetics. Using a conversion rate of 0.08mg fentanyl: 1mg alfentanil, would equate to 630µg/hr remifentanil: 2500µg/hr alfentanil or a ratio of 1:4. In the absence of reliable or validated conversions for equivalent doses of remifentanil to alfentanil in ICU patients, we chose a conversion rate of 1:4 reflecting the significantly greater potency of remifentanil, but shorter duration of clinical action. This is consistent with most clinical literature, mostly from anaesthesia, where the dose ratio of alfentanil to remifentanil is from 2-10:1. **A ratio of 0.25mg remifentanil: 1mg alfentanil was used.**

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Table A3.1: Summary of conversions to equivalent doses of propofol and alfentanil for use in the DESIST analysis of drug use

Sedatives				
Index drug	Propofol dose	Midazolam equivalent	Dexmedetomidine equivalent	
PROPOFOL	Img	0.1mg	0.00053mg[1]	
Analgesics				
	Alfentanil dose	Fentanyl equivalent	Morphine equivalent	Remifentanil equivalent
ALFENTANIL	1mg	0.08mg	2.5mg	0.25mg

[1]Note 0.53μg in justification

Appendix 4 Scoring systems used for the patient experience questionnaires

THE INTENSIVE CARE EXPERIENCE QUESTIONNAIRE

Scores for each domain are reported as sum scores. The scores for the 7 additional questions are reported separately.

Awareness of surroundings

	All of the time	Most of the time	Some of the time	Rarely	Never
29. I recognised my relatives:	5	4	3	2	1

	All of the time	Most of the time	Some of the time	Rarely	Never
20. I was aware of someone near to me:	5	4	3	2	1

	All of the time	Most of the time	Some of the time	Rarely	Never
23. I knew where I was:	5	4	3	2	1

	All of the time	Most of the time	Some of the time	Rarely	Never
21. I knew what was happening to me:	5	4	3	2	1

	All of the time	Most of the time	Some of the time	Rarely	Never
24. I remember my relatives being with me:	5	4	3	2	1

	All of the time	Most of the time	Some of the time	Rarely	Never
30. I felt safe:	5	4	3	2	1

	All of the time	Most of the time	Some of the time	Rarely	Never
22. I felt I was in control:	5	4	3	2	1

	Strongly agree	Agree	Neither agree/ disagree	Disagree	Strongly disagree
19. I was able to let people know what I wanted.	5	4	3	2	1

	Strongly agree	Agree	Neither agree/ disagree	Disagree	Strongly disagree
13. I have no recollection of being in intensive care:	1	2	3	4	5

Frightening experiences

	All of the time	Most of the time	Some of the time	Rarely	Never
31. I seemed to have bad dreams	5	4	3	2	1

	All of the time	Most of the time	Some of the time	Rarely	Never
28. I felt scared:	5	4	3	2	1

25. I saw strange things:

All of the time	Most of the time	Some of the time	Rarely	Never
5	4	3	2	1

26. I felt helpless:

All of the time	Most of the time	Some of the time	Rarely	Never
5	4	3	2	1

11. I thought I would die:

Strongly agree	Agree	Neither agree/ disagree	Disagree	Strongly disagree
5	4	3	2	1

27. I seemed to be in pain:

All of the time	Most of the time	Some of the time	Rarely	Never
5	4	3	2	1

Recall of experiences

	Strongly agree	Agree	Neither agree/ disagree	Disagree	Strongly disagree
6. I wish I remembered more about it:	1	2	3	4	5

	Strongly agree	Agree	Neither agree/ disagree	Disagree	Strongly disagree
2. Most of my memories of intensive care are blurred:	1	2	3	4	5

	Strongly agree	Agree	Neither agree/ disagree	Disagree	Strongly disagree
9. I wish I had known more about what was happening to me:	1	2	3	4	5

	Strongly agree	Agree	Neither agree/ disagree	Disagree	Strongly disagree
15. I seemed to sleep too much:	1	2	3	4	5

	Strongly agree	Agree	Neither agree/ disagree	Disagree	Strongly disagree
5. I never knew whether it was day or night:	1	2	3	4	5

Satisfaction with care

	Strongly agree	Agree	Neither agree/ disagree	Disagree	Strongly disagree
7. My care could have been better:	1	2	3	4	5

	Strongly agree	Agree	Neither agree/ disagree	Disagree	Strongly disagree
18. I thought my care was as good as it could have been:	5	4	3	2	1

	Strongly agree	Agree	Neither agree/ disagree	Disagree	Strongly disagree
16. I was constantly disturbed:	1	2	3	4	5

	Strongly agree	Agree	Neither agree/ disagree	Disagree	Strongly disagree
12. It was always too noisy:	1	2	3	4	5

These items do not belong in any domain, but are reported descriptively.

17. I was given choices about what was happening to me

14. I was glad to be transferred out of intensive care

10. I felt I needed to be in intensive care longer

8. My memories of intensive care are frightening

4. It was upsetting to see what happened to the other patients

3. I was given information I could understand

1. It was a very restful environment

THE IMPACT OF EVENTS SCALE REVISED

Below is a list of difficulties people sometimes have after stressful life events. Please read each item, and then indicate how distressing each difficulty has been for you DURING THE PAST SEVEN DAYS with respect to _____, which occurred on _____. How much were you distressed or bothered by these difficulties?

Item Response Anchors are 0 = Not at all; 1 = A little bit; 2 = Moderately; 3 = Quite a bit; 4 = Extremely.

The Intrusion subscale is the **MEAN** item response of items 1, 2, 3, 6, 9, 14, 16, 20. Thus, scores can range from 0 through 4.

The Avoidance subscale is the **MEAN** item response of items 5, 7, 8, 11, 12, 13, 17, 22. Thus, scores can range from 0 through 4.

The Hyperarousal subscale is the **MEAN** item response of items 4, 10, 15, 18, 19, 21. Thus, scores can range from 0 through 4.

The Total score is the sum of all responses

1. Any reminder brought back feelings about it.

2. I had trouble staying asleep.

3. Other things kept making me think about it.

4. I felt irritable and angry.

5. I avoided letting myself get upset when I thought about it or was reminded of it.

6. I thought about it when I didn't mean to.

7. I felt as if it hadn't happened or wasn't real..

8. I stayed away from reminders of it.

9. Pictures about it popped into my mind.

10. I was jumpy and easily startled.

11. I tried not to think about it.

12. I was aware that I still had a lot of feelings about it, but I didn't deal with them.

13. My feelings about it were kind of numb.

14. I found myself acting or feeling like I was back at that time.

15. I had trouble falling asleep.

16. I had waves of strong feelings about it.

17. I tried to remove it from my memory.

18. I had trouble concentrating.

19. Reminders of it caused me to have physical reactions, such as sweating, trouble breathing, nausea, or a pounding heart.

20. I had dreams about it.

21. I felt watchful and on-guard.

22. I tried not to talk about it.

Total IES-R score:_____

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