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TITLE: Process Evaluation of the A2B randomised controlled trial: an exploration of the factors influencing successful implementation, delivery, and outcomes in an intensive care sedation study.

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ABSTRACT

Background: Choice of sedation of critically ill patients is a core element of intensive care practice. The A2B trial tested the effectiveness of two alpha agonist sedatives versus propofol in reducing time on mechanical ventilation in 38 intensive care units (ICUs) in the United Kingdom (UK). To evaluate both how this complex trial was implemented and how this may have influenced trial outcomes, an understanding of the contextual and practice variation across multiple sites was required.

Aim and Objectives: The aim of this process evaluation of the A2B trial was to determine how the intervention was delivered, the extent to which it was delivered as intended, and the impact this had on outcomes. Specifically, we aimed to:

1. Establish the degree to which the A2B intervention was delivered as intended, specifically in relation to fidelity, dose and reach across patients.
2. Understand factors that impacted on successful delivery of both the A2B intervention and trial, in relation to attitudes and perceptions of staff, including context and standard care.

Design and methods: A mixed-methods, multi-phase design was used following extensive pre-trial exploration of current practice. Quantitative data were drawn from the main trial database covering 38 sites to assess the intervention's fidelity, dose and reach in each site. Data were analysed descriptively and provided a low-moderate-high rating. Qualitative data were collected by interviews mid-trial (phase 1) and end of trial (phase 2). Participants were recruited from a random sample of 30 ICUs active at the time of sampling and included the principal investigator, research nurses and clinical staff. Semi-structured interviews, informed by the trial's logic model, lasted 45 – 60 minutes. Data collection focused on whether the intervention could be delivered as intended, factors that impacted upon successful delivery and understanding intervention adherence. Analysis used a framework approach based on the logic model. Data collection and qualitative analyses were completed prior to knowing the primary results of the trial.

Results: Site intervention adherence ratings for fidelity, dose and reach were low (4), moderate (20) and high (14). Participants from 12 ICUs in each of Phase 1 (33 staff) and 2 (36 staff) provided qualitative data; participating ICUs differed between phases. Factors identified in Phase 1 focused on intervention delivery and trial conduct and incorporated both organisational and participant-related factors. In Phase 2 participant-related factors included clinician preference, individual equipoise, clinician resistance and staff capability and capacity, while A2B trial-related factors included concerns relating to safety and side effects, overnight deep sedation practice, patient comfort and trial documentation. Many of these factors were impacted by the COVID-19 pandemic, particularly in regard to staffing numbers and experience.

Limitations: Due to the impact of the COVID-19 pandemic most data collection occurred remotely through video-conferencing rather than planned at site observation and interviews.

Conclusion: Optimal sedation practice is influenced by multiple factors related to clinician perceptions, capacity and capability. Priorities in care focus on short term safety and comfort. Limitations in staffing mean that longer term consequences related to recovery and rehabilitation are second tier considerations.

Future work: Findings highlight the multiple contextual factors, including both organisational and participant-related characteristics, that should be considered when planning both clinical trials and changes to routine care. Multiple strategies for achieving behaviour change when implementing complex interventions are essential.

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Trial registration number: NCT03653832

Plain Language Statement

Patients in the intensive care unit (ICU) receive pain-killers and sedatives to keep them comfortable and reduce pain. However, some patients are more deeply sedated than needed, and improving sedation and pain management is difficult. The A2B trial compared the usual sedative prescribed in ICU (propofol) with medications called 'alpha-2 agonists' that have both sedative and pain-killing actions. We wanted to see if patients were more awake and comfortable with alpha-2 agonists and whether they came off the breathing machine quicker.

Alongside the trial we conducted a process evaluation to evaluate if study sedatives were given to patients as intended. We also wanted to evaluate if the usual sedative practice, staffing and other considerations affected how nurses and doctors delivered the sedatives. We conducted interviews with nurses and doctors who cared for trial participants, and the research nurses and doctors involved in the trial to find out their opinion. Interviews were conducted mid-way through (phase 1) and at the end (phase 2) of the trial.

Data showed that from 38 ICUs, 34 complied with delivering the sedation care as it was intended to a high or moderate level. Interview topics from 33 staff in 12 ICUs (phase 1) provided a picture of how the sedative medicines were delivered to patients and how the A2B trial was implemented. Interview topics from 36 staff in 12 ICUs (phase 2) described the clinicians' sedative preferences, their level of comfort with uncertainty, any resistance they had to the trial, and staff skills and knowledge. Other topics involved concerns about patient safety, possible side effects, practices for deep sedation overnight, patient comfort, and management of trial paperwork.

We concluded that sedation practice depends on factors related to clinical staff's opinions, staffing levels, and skills. The priorities for care raised by participants are patient safety and comfort.

BACKGROUND

Sedation of critically ill patients is a core element of intensive care (ICU) practice, which aims to enable patients to tolerate mechanical ventilation and other care, minimise discomfort, promote sleep and avoid agitation. Deep sedation is associated with poorer short-term outcomes,¹ but lighter sedation may be deleterious, including long-term psychological well-being.^{2, 3} Propofol is recommended in guidelines as a first line sedative, typically alongside an intravenous opioid infusion.⁴ The alpha-2 agonist dexmedetomidine is also widely used internationally. Clonidine, an older alpha-2 agonist with much lower alpha-2-receptor selectivity, is used widely in the UK.⁵ Alpha-2-agonists are reported to enable light sedation with easily arousable patients and unlike propofol also have analgesic properties, that could limit opioid use although evidence is inconclusive.^{6, 7} The '*Alpha-2 agonists for sedation to produce better outcomes from critical illness (A2B)*' multisite open-label 3-arm randomised controlled trial was designed to examine the effectiveness of dexmedetomidine or clonidine, compared to usual sedation practice (propofol). Patients were randomised to receive either dexmedetomidine-based sedation or clonidine-based sedation or usual (propofol-based) sedation as their primary sedative. The primary outcome was 'time to successful extubation'. A range of hospital-based secondary outcomes were measured, including mortality, time to ICU discharge, measures of sedation quality, rates of delirium, and rates of daily cardiovascular adverse events (severe bradycardia, cardiac arrhythmias, and cardiac arrest).

Given the complexity of ICU sedation practice, the contextual differences between ICUs, and likely variations in both organisational (i.e. unit culture and structure, resources) and participant-related factors (i.e. usual practice, clinical decision making, perceptions of risk), multi-centre trials such as this require exploration of the context and assessment of intervention fidelity to better interpret the findings. For the A2B trial, we embedded a bi-phase process evaluation to assess variation and perceived impact of the above factors when implementing a three-arm sedation interventional trial and the likely impact of this on trial outcome.

AIMS AND OBJECTIVES

The purpose of the process evaluation was to determine how the intervention was delivered, the extent to which it was delivered as intended, and the impact this had on trial outcomes. The specific aims of the A2B process evaluation addressed in this publication were:

1. To establish the degree to which the A2B intervention was delivered as intended, over time and between ICUs, specifically in relation to fidelity, dose and reach across patients.

2. To understand factors that impacted on successful delivery of both the A2B intervention and trial, over time and between ICUs, with specific focus on attitudes, perceptions and context, including standard care (i.e. propofol based sedation).

METHODS

Design

A mixed-methods, multi-phase design was used. We followed MRC guidance to plan, design, conduct, analyse and report the process evaluation.⁸ A logic model was developed for the A2B intervention to guide the process evaluation (Figure 1). The model displays the main components of the intervention and the assumptions by which the components work to achieve trial outcomes. The process evaluation evaluated the validity of the assumptions shown in the logic model in the interviews with ICU staff. To assist with planning the A2B trial and embedded process evaluation, extensive pre-trial exploration of the current UK critical care setting was undertaken. This involved understanding organisational and participant-related factors that had potential to impact delivery of the A2B intervention and wider trial processes. Details of this pre-trial exploration have been reported⁹ and were used to inform the methodology of the process evaluation.

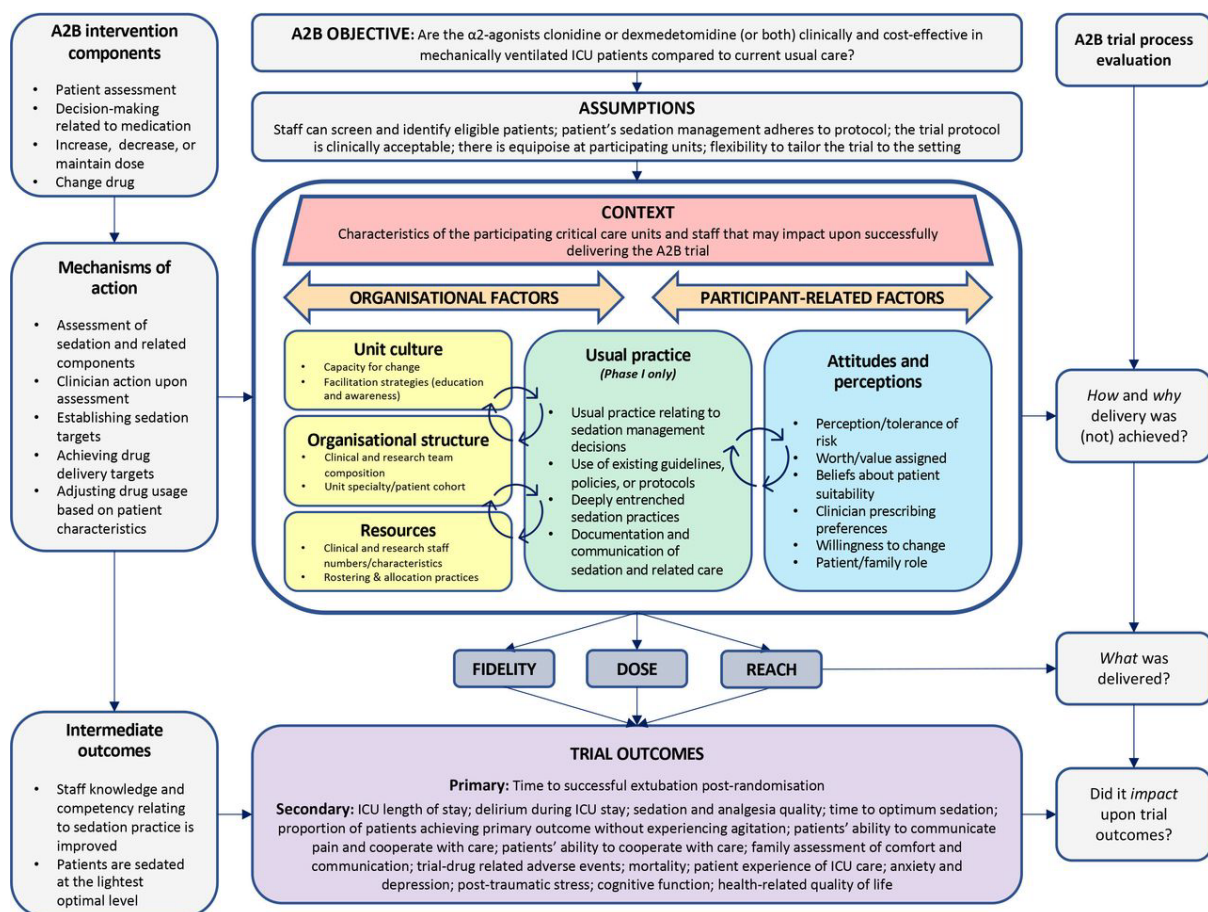


Figure 1: A2B (alpha-2 agonists for sedation in critical care) logic model (this figure is reproduced from an Open Access article previously published by the research team (see Aitken et al. 2024, BMJ Open⁹) This article is published under license to BMJ. This is an open-access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits the author and any non-commercial bodies to reuse the material in any non-commercial way they choose under the terms of the licence, without acquiring permission from BMJ (see: <http://creativecommons.org/licenses/by-nc/4.0/>).¹.

Data collection

Participants

For quantitative analysis, data from all patients (n=1437) enrolled in the A2B trial were extracted from the trial database. For qualitative analysis, although 38 units recruited patients to the trial, 30 were active at the time of sampling for Phases 1 and 2 of the process evaluation. Participants were individuals integral to the implementation and delivery of the A2B trial and/or intervention. Inclusion criteria were: Principal Investigator (PI) at each unit; research nurses responsible for coordinating implementation (≥ 1 at each unit); and clinical staff responsible for delivering the intervention to patients (2-4 per unit). Where the term 'clinician' is used throughout this paper it refers to any health care professional from any discipline involved in clinical care of ICU patients; 'nurse' refers to any member of the nursing team; 'consultant' refers to ICU medical consultant. Where results relate to specific sub-groups of participants the additional detail is provided. The PI and research nurse were responsible for recruiting members of the clinical and research staff and negotiating suitable times for interview. Interviews were conducted online using videoconferencing software (Microsoft Teams), lasted 45-60 minutes; were recorded using an encrypted recorder; and transcribed verbatim by a study sponsor approved transcription company.

Throughout trial: quantitative data

Details of the main A2B trial are published elsewhere including the protocol⁴ and the results.¹⁰ Briefly, data collected on a daily basis included sedatives administered, frequency of assessment and sedative depth using the Richmond Agitation-Sedation Scale (RASS) and number of eligible patients recruited. These were used to understand intervention and recruitment compliance.

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop

new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data is used. #datasaveslives You can find out more about the background to this citation here: <https://understandingpatientdata.org.uk/datacitation>

Phase 1: mid-trial qualitative data

During Phase 1, multi-disciplinary clinicians were interviewed to explore whether the intervention could be delivered as intended and factors that impacted upon successful delivery. Semi-structured interview guides, informed by the logic model and pre-trial data, were used. Data collection commenced once units had been recruiting patients for at least 3 months to ensure exposure to the intervention. Pre-trial data were used in combination with unit-level factors to develop a sampling matrix and select a purposive sample of units for participation in Phase I. Each unit was allocated to the matrix according to 4 characteristics: i) recruitment rate, ii) usual practice relating to sedation target use, iii) ICU-specific research nurse resource, and iv) unit size. Units were allocated anonymous identifiers and selected from the matrix by an independent member of the research team.

Phase 2: end of trial qualitative data

Phase 2 involved in-depth semi-structured interviews within the last 6 months of the trial with clinicians from a range of disciplines. Units were sampled in the same manner as Phase 1. However, only units that had enrolled patients into A2B within 3 months prior to being contacted were selected, to optimise recall of factors related to intervention delivery. Interview data were used to explore organisational and participant-related factors that acted as barriers or facilitators to successful intervention and trial delivery. They also explored reflections on use of the trial protocol, medications, and clinical decision-making processes.

Patient and public involvement (PPI)

Former ICU patients and family members were involved at multiple points of the trial design and conduct including the embedded process evaluation. One member of the PPI group was a co-applicant on the grant application and advised the Trial Management Group, where the plan and results of the process evaluation were discussed on an ongoing basis, throughout the trial. A former patient was an independent member of the Trial Steering Group.

Equality, Diversity and Inclusion (EDI)

This pre-planned process evaluation was part of the overall A2B trial programme of work. We reflect on EDI in several important areas: project focus, research team, and PPI involvement. We also reflect on the weaknesses and areas for improvement based on the trial. Of relevance, the INCLUDE framework ([INCLUDE - Guidance \(google.com\)](#)) post-dates the funding and planning of the A2B trial. The A2B trial was a commissioned call, and as such had progressed through NIHR prioritisation processes. The brief stipulated the intervention ('alpha2-agonists'), the patient groups ('adults admitted to ICU who require mechanical ventilation'), the setting ('intensive care'), and a range of important outcomes. Intensive Care is a service/place and not a disease, and we recognised the need to define the population carefully to include patients for whom sedation may have the greatest clinical impact. ICU populations are heterogeneous in multiple domains, including demographics, pre-existing health, and illness aetiology and severity. ICU services may also vary in their structure, staffing, and culture.

We believe we recruited a diverse heterogeneous population typical of UK critical care. Specifically, the age and gender profile were typical of populations described in national audits. Importantly, we included patients with significant co-morbidity, also typical of UK ICU admissions. The majority of patients were emergency/unscheduled admissions, with a 'medical'/'surgical'/'trauma' split similar to UK audit data. Because recruitment occurred *after* ICU admission, the population had already been 'selected' as appropriate for ICU care based on clinical practice, so that although some patient groups would not be included, for example severe frailty, this was representative of standard NHS care. Our inclusion criteria were very broad and focussed on the need for ICU sedation and likely longer periods of MV; as such they were unlikely to exclude under-served groups. The exclusions were mainly related to brain injury, because for these patients the exposure-outcome relationship was likely to be dominated mainly by the underlying condition. We are clear that our conclusions should not be applied to this or other excluded groups.

We included >40 ICUs across the UK (around 15% of all ICUs), which were from all geographical regions including all four nations. ICUs were also from a mixture of academic and other tertiary hospitals, through to smaller district general hospitals. Served communities included diverse populations in terms of socio-economic status, ethnicity, and urban/rural setting. This also applied to the staffing of the services, which is relevant given the key input from clinical staff delivering the intervention. The sampling of ICUs undertaken for the PE ensured we captured relevant diversity across these issues both in terms of setting and the staff interviewed. We did not record ethnicity or socio-economic status for patients in the A2B study, or for interviewees in this process evaluation, which was a weakness of our data collection.

Our research team included diverse clinicians involved in care (ICU doctors, elderly medicine doctors, nurses, pharmacists), although we did not include physiotherapists, occupational therapists or psychologists who may have added additional value. We included senior academics, but some co-applicants were junior academic and clinical investigators. We had an active Associate PI programme which provided experience and training opportunities. Patients were involved throughout our work. However, we did not proactively seek PPI involvement from diverse groups relevant to EDI, and future research should consider this.

Finally, our embedded process evaluation specifically considered the context of the research, and acquired data from a diverse range of clinical and research staff in participating sites. The focus of these interviews, which included a range of domains relevant to designing, conducting and interpreting ICU sedation (and other) trials, has provided rich additional data to help us understand our findings and their relevance to future practice.

Data analysis

The analysis sought to identify the extent to which the A2B intervention was implemented as intended, and barriers and facilitators of implementing and delivering the A2B trial and intervention. The data were used to inform interpretation of the main trial's findings for the primary and secondary outcomes. Data collection and qualitative analyses were completed prior to knowing the primary results of the trial to ensure blinding to the trial outcomes.

Quantitative data extracted from the main A2B trial database were summarised descriptively and each study site was assigned a Red-Amber-Green (RAG) score based on level of adherence for each of the following measures of intervention delivery outlined by Moore et al:⁸

- Fidelity: % of patients with correct treatment every day during first 4 days
- Fidelity: % of patients with RASS -2 or lighter at any point during first 4 days
- Dose: % of patients with RASS assessment at least once per day during first 4 days
- Reach: % of eligible patients proceeding to randomisation.

RAG scores were 0: <40% adherence; 1: 40–59% adherence; 2: 60–79% adherence; and 3: ≥80% adherence. Scores for each adherence parameter listed above were then summed to create total RAG scores for each study site, with equal weighting given to each adherence parameter. Measuring reach across staff was planned but not able to be achieved.

Interviews were analysed using a 7-step Framework approach.¹¹ This involved coding data using a deductive analytical framework which allowed for themes emerging from the data to be used as indexing categories. Conducting a deductive thematic analysis using a pre-defined theoretical framework, allowed in-depth understanding and exploration at Phase II of the concepts of interest identified in Phase I.

The analytical framework was applied to a sample of transcripts, and a second researcher reviewed the thematic framework as applied to the data. Data were then mapped onto the framework. Unallocated data were examined inductively, and revised iteratively until all data were allocated. The research team discussed the codes and themes to achieve consensus, and interpretation of the data was reviewed to construct overall explanations. An advantage of the framework approach was that researchers' interpretations of participants' experiences were transparent. This approach to analysis was useful because of the large dataset, as it provided an intuitively structured overview of all summarised data with a clear audit trail from raw data to the final themes. Results from the quantitative and qualitative components were then synthesised to inform understanding of the extent and challenges in implementing the A2B intervention.

RESULTS

Trial recruitment took place between December 2018 and October 2023.

Quantitative data

Implementation of the A2B trial intervention was summarised against intervention characteristics including fidelity, dose and reach (Table 1, Figure 2 and Supplementary Materials 2). The percentage of patients at each site with the correct treatment administered every day during the first 4 days ranged from 0–100%. The percentage of patients with RASS \geq -2 at any point during the first 4 days ranged from 40–100%. The percentage of patients with a RASS assessment at least once per day during the first 4 days ranged from 67–100%. The percentage of eligible patients proceeding to randomisation ranged from 7–100%. Overall RAG scores ranged from 6–12 with 14 sites (37%) rated high adherence (RAG 10–12), 20 sites (53%) rated moderate adherence (RAG 8–9) and 4 sites (11%) rated lowest adherence (RAG 6–7). Overall, 9 sites randomised fewer than 10 patients (<5 patients in 3 sites); the 4 sites with lowest adherence were all in this group.

Table 1: RAG scores of A2B implementation characteristics (n = 38 sites [29 sites enrolled \geq 10 patients])

	RAG Score	0 (<40%)	1 (40–59%)	2 (60–79%)	3 (≥80%)
Implementation characteristic					
Fidelity: % of patients with correct treatment every day during first 4 days		1 site [Nil]	Nil	14 sites [11 sites]	23 sites [18 sites]
Fidelity: % of patients with RASS ≥-2 at any point during first 4 days		Nil	1 site [Nil]	11 sites [9 sites]	26 sites [20 sites]
Dose: % of patients with RASS assessment at least once/day during first 4 days		Nil	Nil	2 sites [Nil]	36 sites [29 sites]
Reach: % of eligible patients proceeding to randomisation		16 sites [11 sites]	9 sites [8 sites]	9 sites [8 sites]	4 sites [2 sites]

RAG: Red-Amber-Green; RASS: Richmond Agitation-Sedation Scale. Number in brackets excludes sites with fewer than 10 patients.

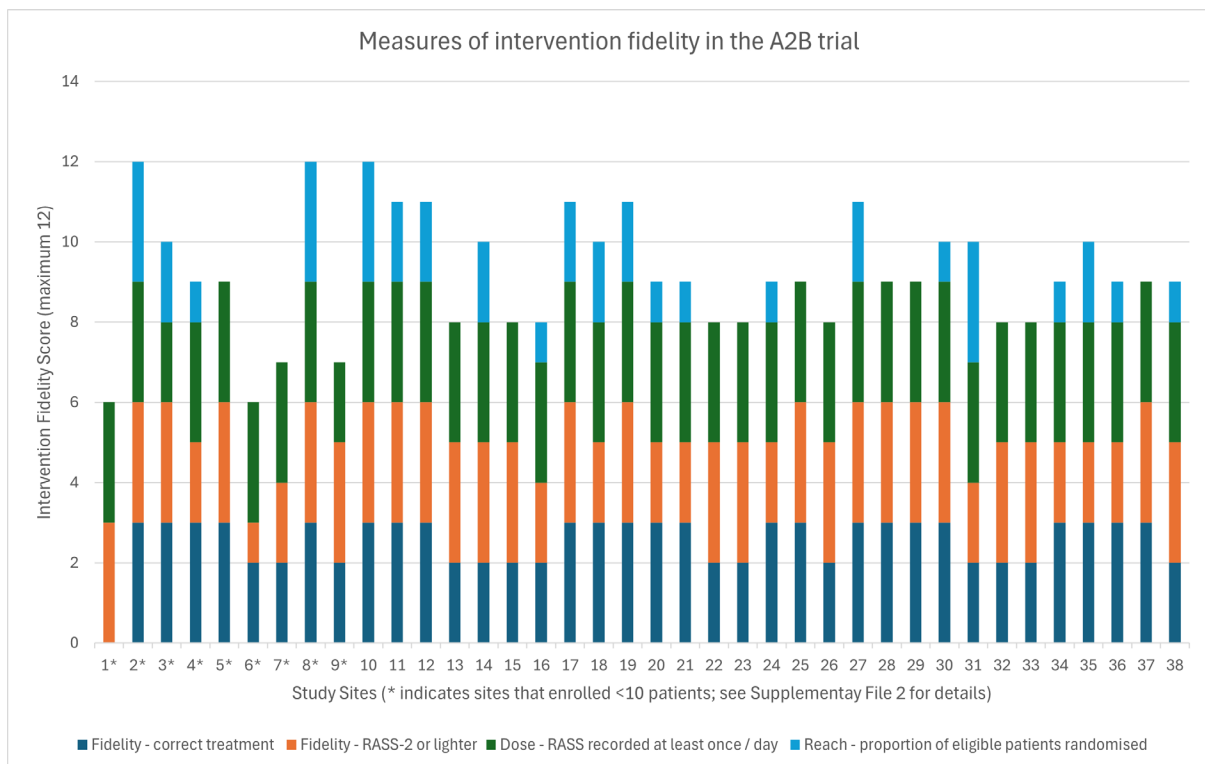


Figure 2: Measures of intervention fidelity in the A2B trial

Qualitative data

Phase 1

Phase 1 data were collected January-April 2023. Twelve ICUs (out of 30 active units) were purposively selected (based on recruitment rate, routine use of sedation targets, research nurse numbers and unit size) to ensure a maximum variation sample. Thirty-three staff participated in Phase I interviews including 20 research nurses (17 with current or past clinical ICU experience), 5 staff nurses, and 8 PIs (ICU medical consultants working clinically and taking on the role of local site-based PIs). Semi-structured interviews were used to explore emerging issues with intervention delivery, including intervention fidelity, staff perceptions and standard care and identify concepts of interest. Two broad sets of factors emerged during Phase 1: those impacting upon delivery of the intervention, and those impacting on wider trial delivery.

1. Factors impacting intervention delivery

- a. Organisational factors: Research nurse/team support; usual practice including the presence of a sedation policy or guideline.
- b. Participant-related factors: Risk perceptions; skill mix.

2. Factors impacting the trial delivery

- a. Organisational factors: COVID-19; resources.
- b. Participant-related factors: Family participation; the SPICE III trial;⁷ individual equipoise and knowledge deficits.

Factors identified during Phase I were used to inform subsequent development of study implementation materials, and were explored in more depth during Phase 2 data collection – consequently these factors have not been described in greater detail here. It should be noted that the results of the SPICE III trial⁷ were released during the early phase of conducting the A2B trial. In summary SPICE III demonstrated a similar 90-day mortality rate in patients receiving dexmedetomidine and usual sedation, but raised questions in a prespecified subgroup analysis about differential effects on mortality across age-groups, with higher mortality in younger patients and lower mortality in older patients.^{7, 12}

Phase 2

Phase 2 data were collected September-December 2023. Fifteen ICUs (out of 30 active units) were purposively selected from the sampling matrix to ensure a maximum variation sample. Of these, three units declined to participate due to staffing and workload issues. Thirty-six staff participated in the Phase 2 interviews across the 12 ICUs comprising 20 research nurses (almost all of whom had clinical ICU experience), 5 staff nurses, 10 PIs, and 1 clinical trials assistant. Phase 2 interviews focused on uncovering factors relating to the trial, staff and organisations that may have acted as barriers or

facilitators to successful intervention and trial delivery. They also explored reflections on use of the trial protocol and trial medication, and clinical decision-making processes. Two broad sets of factors emerged during Phase 2. Theme 1 included factors related to clinicians and research nurses participating in the process evaluation and included a) clinician preference, b) individual equipoise, c) clinician resistance, and d) staff capability and capacity. For the purposes of this process evaluation participants are the clinical and research staff who were interviewed in each of the phases. Theme 2 included factors that specifically concentrated on the implementation and delivery of the A2B trial and included a) concerns relating to safety and side effects, b) overnight deep sedation practice, c) patient comfort, and d) trial documentation. Detailed quotes related to all factors are located within Supplementary Materials 3.

Participant-related factors

Participant-related factors included clinician preference, individual equipoise, clinician resistance and staff capability. Clinician preference related to the preference for one sedative agent over another, and their perception of the impact of alpha-2 agonist use in usual practice on uptake of the new intervention. Individual equipoise focused on the presence or absence of equipoise by each individual clinician and how that impacted on implementation of the A2B intervention and was closely connected to clinician preference. Clinician resistance related to change in what and how sedatives were used and included resistance to use of specific A2B medications in some patient sub-groups. Staff capability related to experience in using alpha-2 agonists, titrating and weaning sedation as well as the influx of new and inexperienced staff during and after the COVID-19 pandemic, and the impact of research team support.

Clinician preference

Staff at half of the units reported that there was no preference for one sedative over another. This was attributed to both dexmedetomidine and clonidine being routinely used in practice in many ICUs, usually as an adjunct when waking or weaning agitated patients. This meant that, although alpha-2 agonists were not normally used as first line sedatives, nurses were familiar with the medications and were confident titrating them according to the protocol. When asked their preferences between alpha-2 agonists, staff at one third of units reported a preference for clonidine over dexmedetomidine, with the remaining staff describing no preference. This was predominantly the view of bedside nurses because they perceived that patients had less bradycardias when receiving clonidine.

"...they're probably happier with clonidine. But you just get less bradycardia with it... even though that might end up being an important result... it's definitely the dex arm that's been the most challenging..." PI06/11

However, staff at two units reported that familiarity with alpha-2 agonists and their use in usual practice sometimes posed a challenge to protocol adherence when patients were randomised to propofol. Usual non-trial practice involved introducing an alpha-2 agonist alongside propofol when weaning agitated patients and PIs discussed how it was difficult to not do this when patients were enrolled in the trial. This led to protocol deviations by the introduction of alpha-2 agonists when patients had been randomised to the propofol arm. A PI at a third unit indicated the focus on lighter sedation was much easier when patients were not randomised to propofol. They felt familiarity with propofol as a first-line sedative prevented clinicians from adhering to the protocol and challenged their tendency to over-sedate patients. In contrast, a small number of clinicians found it easier to focus on the aim of the trial and adhere to the protocol when patients were randomised to either alpha-2 agonist.

"I think the only danger with the propofol is... there's just a tendency and a global tendency to over sedate patients. I think on the treatment arms if you like, maybe there's a little bit more focus. But sometimes on the propofol arm, it's easy just to sit back... a side effect almost of the fact that people are doing what they normally do... rather than trying to hit the RASS." PI05/19

Staff at one third of units reported a preference for usual care (propofol). This opinion was held predominantly by bedside nurses who preferred the medication they were most familiar with, and a preference for the rapid onset somnolence and sedation that propofol offers. Furthermore, they also described a lower tolerance for risk and thus patients were more deeply sedated than mandated in the protocol by supplementing the alpha-2 agonists with additional propofol.

Individual equipoise

Staff at over half of the units reported equipoise related to sedative use, while staff at a third of units said there was not sufficient individual equipoise on this topic at their unit to deliver the trial without clinician resistance. The core reasons related to preference for, or personal dislike of, specific medications, with examples including:

- In a unit with a high proportion of cardiac intensive care consultants it was perceived they had a lower threshold for risk relating to cardiovascular instability and thus reticence to have patients on alpha-2 agonists as first line sedation

- A consultant who voiced a strong dislike of dexmedetomidine and had a very low threshold for stopping trial medications in A2B patients if they deteriorated, with no patients recruited to A2B when this consultant was on duty
- Medical doctors at more than half the sites had strong preferences for usual care
- A consultant on the delegation log who lacked individual equipoise and wanted to use whichever medication they believed was most suitable for certain patients/groups. This presented recruitment challenges with limited recruitment proceeding.
- A perception by those interviewed that nurses had very strong preferences for usual care.

Research nurses at two units disclosed a broad dislike of dexmedetomidine amongst both nursing and medical colleagues:

"...we have to tell them, you know, we can't choose, it's randomised by computer, so they could go into propofol, clonidine or dexmedetomidine, and they're like, oh if there's a risk they're in Dex, absolutely not" ResN05/02

Clinician resistance

Staff at two thirds of units reported clinician resistance at consultant-level. There were three core reasons that consultants either openly opposed or did not engage with A2B: resistance to change, resistance to including some patient sub-groups, or resistance to using a specific medication or regimen.

1. Resistance to change

Research nurses and PIs at a third of units reported consultants who were not willing to engage with the A2B trial or permit patient recruitment when they were the clinical lead because they preferred usual practice. Staff at one unit described how some consultant colleagues were generally less engaged with research as a whole. When these clinicians were on duty it was unlikely that patients would be recruited into A2B, or to other studies. One of these units also experienced resistance from the nurses working at the bedside, with research nurses describing negativity towards research:

"...they're set in their ways, they want to keep them on propofol and alfentanil. So, there would be a portion of patients who weren't recruited just because the consultant refused, even though they were eligible, so...they don't necessarily even have to give a reason, they just say, no." PI08/23

2. Resistance to including some patient sub-groups in A2B

Research nurses at two units discussed how some consultants were resistant to recruiting patients with bowel-related issues. They described how, although patients were eligible to participate, these consultants had a high threshold for recruiting patients and a low threshold for withdrawing this subgroup of patients from the study. One discussed how they perceived hypervigilance for bowel-related complications when patients were randomised to alpha-2 agonists – this vigilance was less evident in non-trial patients.

3. Resistance to specific drug/regimen in A2B

PIs at two units described how some consultants disliked having to commit to a specific medication regimen within the trial, and not have the autonomy to make decisions on a case-by-case basis. This related partly to the choice of multiple sedatives in challenging patient groups, and partly to being able to adequately control patients and their sedation:

“...you could have had somebody who was an alcoholic and you wanted to have all the options for sedation, you didn’t want to have your hands tied in a difficult to sedate patient... you know, you wanted to discuss it with the team and they didn’t want to have their therapeutic armamentarium, you know, limited because the patient would end up... might be randomised to no alpha 2 agent.” PI03/32

Staff capability and capacity

Staff at most units reported that both senior and more experienced staff nurses were more competent and confident caring for A2B patients. They discussed four main factors relating to staff capability and capacity which impacted their ability to deliver the intervention: experience using alpha-2 agonists, experience titrating and weaning sedation, the COVID-19 pandemic influx of inexperienced staff, and research team support.

1. Experience using alpha-2 agonists

Staff at two units discussed how less experienced staff nurses appeared to struggle when allocated patients randomised to alpha-2 agonists. Although these medications were used routinely in clinical practice, they were not first line sedatives and less experienced nurses required support and education to optimise adherence with the protocol. Experienced staff nurses were more comfortable changing medications and titrating sedation in accordance with bedside algorithms because they have had more experience with ICU medications, and more autonomous experience assessing and weaning patients:

“...in this case I think it was definitely because of the clinical experience the nurse had. They were very comfortable with the drugs... very comfortable weaning and assessing the patient... Whereas if you’ve got a junior band five who’s absolutely terrified on a daily

basis at the bedside and they haven't quite developed the skills to be comfortable in changing medication like an experienced band six would be." PI01/26

2. Experience titrating and weaning sedation

Both clinical and research nurses described how seniority and experience of bedside nurses correlated with confidence when caring for patients randomised to alpha-2 agonists. The more experienced the bedside nurse the smoother the process of delivering the intervention. Staff noted that even if experienced nurses were not familiar with using alpha-2 agonists in this manner experience gave them the confidence to deal with unpredictable or challenging situations which may arise:

"Like the more experienced you are, the more confident in it, I suppose. And the more exposure you've had to sedated patients as a whole, the more confident you are with your sedation" RN01/15

3. COVID-19 pandemic influx of inexperienced staff

Staff at around half of all units discussed the detrimental impact the COVID-19 pandemic had on staff retention, and the subsequent influx of new and junior nurses. They felt strongly that this significantly impacted upon nurses' capabilities to deliver the A2B intervention as intended, both because of a lack of experience of using alpha-2 agonists, and a lack of experience in titrating and weaning sedation. In addition, both PIs and research nurses described how sedation practice during the pandemic changed whereby patients with COVID-19 were commonly deeply sedated using non-routine drugs (such as midazolam) due to medication shortages and need for deep sedation. This deep sedation practice commonly crossed over into all patients and proactive titrating and weaning from sedation did not happen.

At the same time, the new junior and inexperienced nurses who started working in ICU during this time had only witnessed deep sedation practice, often with no previous experience of nursing lightly sedated patients and autonomously titrating and weaning sedation. These two factors in combination meant this group of nurses considered deep sedation practice normal and found it challenging to change in the post-pandemic context:

"So COVID... a culture of deeper sedation slipped in and there were many reasons for it, but also so did lots of ARDS, and then also things like drug unavailability... Another thing that changed quite a bit is nursing contingent. We lost quite a lot of our very senior nurses so we had suddenly quite a few more junior nurses and some of them came in during the time when the sedation was deeper. So that made quite a big difference." PI09/27

Participants perceived competence in different ways. Staff at three units felt clinical competence to deliver the A2B intervention was not related to seniority or experience, but that it was more dependent on the personality of the bedside nurse or that nurse experience or grade was not a relevant factor for delivering this trial. This was because, in many ICUs, nurses at the bedside were heavily supported by the research nurse team (all of whom were senior ICU nurses), who conducted the majority of the work and intervention delivery.

4. Research team support

All units reported that the research team provided substantial support to bedside nurses. This support included clinical bedside support by research nurses, use of bedside education and reminders, and PI/associate PI presence. This was primarily enabled by every unit having at least one research nurse with previous clinical ICU experience. Only 1 unit reported serious organisational capacity issues which directly impacted their ability to deliver the trial. They operated 3 separate ICUs within 1 Trust, with both research nurse and clinical staff working across all sites. They described issues with nurse retention and high staff turnover, high sickness rates, and widespread staffing challenges. Delivering on research was considered an additional onerous burden on staff.

Research nurses with clinical ICU experience were able to prepare and administer trial medication for bedside nurses. They often stayed until an appropriate rate and dose had been achieved and, when randomised to either alpha-2 agonist, they encouraged down-titration of propofol. Research nurses viewed this as critical to optimising protocol adherence, as it took pressure off the bedside nurses:

“As you know research nurses are the actual linchpins in the process.” PI09/27

Research nurses also provided education to bedside nurses when caring for A2B patients. This was an effective approach to educating appropriate staff and maintaining trial awareness. Many units reported high turnover and so having infrequent larger scale teaching sessions was not efficient in maintaining awareness due to infrequent A2B patients. Many research teams developed methods of reminding bedside staff that patients were in A2B. This included brightly coloured reminders in patients' notes, signage, and pre-prepared packs containing relevant paperwork and contact information for nurses.

Staff at a third of units reported having either a PI or associate PI who collaborated closely with the research nurse team to optimise engagement and recruitment. Research nurses at one unit discussed how their PI was 'hands on' at the consent and recruitment stage of the study, but this was not described by other units. They perceived that families were more inclined to give consent when the PI or a consultant colleague spoke to them regarding participation, than when a research nurse made the

approach. Staff at three units described how the associate PI scheme improved engagement by the doctors – their more frequent presence and availability to talk to and educate junior doctors boosted study awareness.

A2B trial-related factors

A2B trial-related factors identified included those related to safety and side effect concerns, overnight deep sedation practice, patient comfort, and trial documents. Concerns relating to safety and side effects focused on cardiovascular instability, bowel/ileus concerns, patient agitation/safety, and the implications of SPICE III trial findings relating to dexmedetomidine.⁷ Overnight deep sedation practice related to deeper sedation overnight and the role that staffing and support played. Patient comfort related to the analgesic properties of alpha-2 agonists, and ease or difficulty of managing patient sub-groups. Trial documents related to the importance of supporting paperwork, particularly when research teams were not present on units.

Concerns relating to safety and side effects

Staff at most units discussed safety concerns relating to potential cardiovascular instability from the use of alpha-2 agonists, primarily bradycardia and hypotension. Research nurses described hypervigilance by bedside nurses for bradycardia when patients were randomised to alpha-2 agonists with a perception this hypervigilance was more pronounced in A2B trial patients than other patients:

“There was a lot of fear ...tended only to be around the Dexdor, even though it happened, yes, with clonidine, it tended only to be with the Dexdor, oh but he is bradycardic, or, you can't put him on, his heart rate's only 60... ResN14/38

One PI reported that they planned to continue with usual practice after the trial, regardless of the results because of a dislike of the cardiovascular side effects of dexmedetomidine. Research nurses at another unit described that bedside nurses felt uncomfortable when patients were on clonidine, with the primary concern being hypotension because of previously witnessed episodes. Another research nurse discussed how, having had a (cardiovascular instability) Suspected Unexpected Serious Adverse Reaction (SUSAR), they developed plans, including reassurance and guidance, for the management of future incidents as nurses were reluctant to continue managing patients as per the protocol; this improved subsequent protocol adherence.

Research and staff nurses at over half of the units reported three interconnected safety concerns. These related to i) patients being more awake and potentially agitated and unmanageable; ii) the risk of self-extubation or causing harm; and iii) the lack of support or inadequate staffing to safely manage these incidents. These safety concerns did not relate to a specific study drug, were perceived and did

not arise from actual occurrences. Only one unit reported an incident of self-extubation for a patient randomised to an alpha-2 agonist, this patient was able to maintain their own airway and remained extubated. Ultimately, the fear relating to potential adverse events and the perceived lack of support led nurses to opt for usual care (propofol) and deep sedation regardless of which intervention patients were randomised to. These safety concerns reduced the likelihood of nurses managing patients in accordance with the protocol.

"...you would say to them, ... why did we not do this there, you know, and they always...it's always patient safety overnight, I think a lot of them would give you that, you know, say, but he was agitated through...there's less people around and it's...patient safety would always be brought up as a thing of, but we didn't do it because...to keep the patient safe and agitation." ResN14/38

It should be noted these perceptions of low protocol adherence were generally not reflected in the measure of protocol fidelity.

A PI at one unit discussed how the SPICE III trial results and the formal caution relating to the use of dexmedetomidine in young people had impacted his practice both in A2B trial and usual practice. Elsewhere, another PI described how the same results had no impact upon practice or attitudes towards the trial despite everyone being made aware of the results. This was despite patients in this unit experiencing multiple significant bradycardias and a pulseless electrical activity (PEA) arrest.

"...we certainly discussed it at a local level, so everybody was aware of this potential safety signal, and I think even then people were aware that actually the best way to know if that was true is to enrol into this study. So I think people were cautious and vigilant for complications, but I don't think it put anybody off enrolling." PI01/26

Overnight deep sedation practice

Staff at over half the units reported sedating patients more deeply overnight. Although deep sedation is part of usual practice, it has been included as a trial related factor due to A2B being a trial about sedation. Deep sedation was described as being in the interests of patient safety due to inadequate clinical staffing (numbers and seniority) and associated perceived risks or to prevent patients becoming agitated or unmanageable. There was a perception that propofol infusions were regularly turned up overnight, regardless of which sedative patients were randomised to. This was one of the main factors impacting upon protocol adherence and reduction in sedation level/RASS score. Research nurses felt deep sedation and deviation from the trial protocol was more pronounced overnight partly because there was no research team present to support clinical staff. Bedside nurses corroborated this by

discussing how they were more reluctant to care for A2B patients overnight due to research team absence. Crossover in practice from cohorts of patients who required deep sedation to all patients was another reason for normalisation of overnight deep sedation. A PI at one unit described how they had high numbers of post-operative neurology patients and that the deep sedation practice in those patients tended to be carried over into all patients. However, they also highlighted how participating in the trial made them recognise this and think more about their general sedation practice.

Staff at a second unit discussed how deep sedation happened in the aftermath of the COVID-19 pandemic. They described that nurses were no longer accustomed to having lightly sedated ventilated patients and that practice had not returned to the pre-pandemic methods and the difficulties in implementing change

“But, you know, staff have to get used to patients being awake with a breathing tube, again. You know, for years, it was abnormal to have patients deeply sedated, because we’ve gone past that.” ResN07/30

Patient comfort

There were mixed views about the analgesic properties of alpha-2 agonists and pain management. Staff at over half the units were not aware of the analgesic properties of alpha-2 agonists. They did not adjust normal analgesia practice accordingly, and specifically discussed how normal analgesia practice continued with all 3 sedatives within the trial. Consequently, at these units, staff did not report any differences in patients’ perceived pain whilst sedated on an alpha-2 agonist. Conversely, staff from a quarter of units recognised the analgesic properties of alpha-2 agonists and took steps to address this amongst clinical staff. The research nurses discussed how bedside nurses had a preference to keep fentanyl running alongside the trial sedative. Concerns about patients being in pain or uncomfortable made them reluctant to down-titrate propofol and analgesia:

“And it was also trying to educate them that actually, you know, trying to wean down maybe the fentanyl, because, you know, these analgesic effects from some of those drugs...I mean, I think for the main part, a lot of patients seemed quite comfortable no matter what, you know, sedation they had.” ResN20/17

There were conflicting views about sub-groups of patients who staff felt were either easier or more challenging to manage on first-line alpha-2 agonist sedation. Staff at one unit discussed how they found patients with high alcohol or opioid use pre-admission easier to sedate, whilst staff at two further units reported this sub-group of patients as more challenging to sedate on first line alpha-2 agonists. Staff at an additional two units reported how patients with respiratory failure and those who

were agitated pre-intubation were easier to manage on first line alpha-2 agonists. However, staff at remaining units were unsure what the most suitable patient groups were for adequate alpha-2 sedation, instead believing that alpha-2 agonists worked well on some patients and not others. They described a high heterogeneity and an inability to predict how patients would perform on alpha-2 agonists.

In relation to perceived patient comfort, staff at a quarter of units reported that patients seemed more awake and comfortable on alpha-2 agonist sedation. Specifically, the research and staff nurses discussed how they felt patients were calmer and more consistently comfortable on either of the alpha-2 agonists, in contrast to periods of being either heavily sedated or wide awake when on propofol – staff felt finding the ‘middle ground’ was more difficult in the usual care group. Staff at only one unit described patients on alpha-2 agonist sedation as appearing less comfortable. This was reported by the bedside and research nurses, but the PI felt that there were no observable differences.

Staff at one unit reported an issue related to the usability of dexmedetomidine. The research team felt strongly that it was difficult for bedside nurses to titrate it effectively, and that patients remained agitated despite being on maximum doses. Conversely, a second unit described how, once bedside nurses began to see patients being comfortably sedated on dexmedetomidine, it helped challenge negative opinions and staff began to view it more favourably.

Trial documents

Staff at half of all units cited the bedside algorithm documents provided by trial management as an important tool to optimise intervention delivery, particularly out of hours. However, staff at the remaining units discussed how there was often at least one member of the research team working clinically over the weekend and so there was less dependence on the bedside support tools.

Staff at half of units reported that completing the data collection form each shift was very challenging and burdensome for bedside nurses, primarily because of the heavy workload, and nurses’ perception that research-related documentation was less important than clinical care, observations and documentation. At those units where staff did not report any challenges in shift form completion, it is worth noting that research nurses commonly alluded to assisting with and completing the shift forms on bedside nurse’s behalf; they were often able to gather most of the data for the shift form from the nursing/electronic notes.

Completing the shift form was reported as especially challenging when patients were randomised to receive the usual sedative, propofol. This difficulty persisted even after patients were extubated, as it was not always clear to clinical staff that these patients were participating in an interventional study:

“I think, where we struggled a little bit was when it was standard care, funnily enough. In terms of getting the bedside shift forms completed. I think because it was normal practice, they don't always, you know, remember to do it. And also, when patients are extubated, it's re-emphasising that they're still on the study for another 48 hours.” ResN07/30

DISCUSSION

Sedation practice is a challenging area to research and implement change, however the potential improvements in patient outcome are significant when sedation practice is optimised. Challenges arise due to multiple factors that are created by the focus on patient comfort and the associated emotional elements of staff and family members observing a patient who is agitated or in pain. We identified a range of both patient related and trial related factors that potentially impacted on the conduct of the A2B trial and the extent and fidelity of intended intervention delivery. Strong personal opinions of clinicians regarding effectiveness of pharmacotherapy or sedative strategies and a degree of variation in standard sedation and opioids contributed to implementation challenges and are compounded by challenges of conducting complex critical care trials. In the A2B trial this was further exacerbated by the COVID-19 pandemic. These factors may have contributed to the high number of sites randomising <60% of eligible patients. Despite these difficulties, adherence to the A2B intervention was moderate or high across 90% of the study sites, using the pre-defined metrics chosen, and across all sites recruiting more than 10 patients. The findings of this process evaluation are vital in both addressing how to best implement and sustain evidence-based interventions, as well as how to deliver future sedative and opioid trials in ICU.¹³

In complex and dynamic healthcare environments such as critical care, up to 70% of all change efforts fail to fully implement desired interventions.^{14,15} There are various reasons why results of clinical trials often fail to translate into clinical practice, and critical care research is no different. In this context, understanding the barriers and facilitators to successful delivery of any intervention is essential.

When considering the multiple participant related factors identified, the challenge of addressing clinician behaviour was emphasised throughout the process evaluation. Considerations such as clinician preference, individual equipoise and clinician resistance were largely driven by usual practice, staffs' previous experiences with the medications and sedation management, and whether they had pre-defined ideas and beliefs about treatment preferences. During A2B these factors were exacerbated by the publication of the SPICE III results⁷ mid-trial and questions were raised about the effectiveness and safety of alpha-2 agonists, specifically dexmedetomidine. Clinicians often frame their decision-making around the benefit versus risk of an intervention, including time required, complexity, and competing clinical commitments.¹⁶ The increased mortality reported in younger patients in the

dexmedetomidine arm of the SPICE III trial, along with the subsequent European Medicines Agency advice¹⁷ regarding potential patient harm from dexmedetomidine, concerned clinicians about increased risk of patient harm from early dexmedetomidine use. This likely had an impact upon the degree to which they engaged with the trial and delivered the intervention as intended. As outlined, significant numbers of clinical staff lacked individual equipoise and many units indicated some medical consultants resisted the study. Of interest, the mechanisms of potential harm in younger patients are uncertain, although post-hoc analyses of the SPICE III trial support the hypothesis these may be dose-dependent.¹⁸ For staff, the most 'visible' adverse effects were bradycardia and hypotension, and risks from agitation. These factors likely limited intervention fidelity, but could equally be considered appropriate responses in a pragmatic trial.

The findings from this process evaluation indicated that autonomy in sedative selection by the consultant impacted the decision on whether all eligible patients were recruited into the A2B trial. Staff in six sites raised the issue of inaccuracy in predicting whether a further 48 hours of mechanical ventilation was required and one site conducted a retrospective chart review, finding that 49 of 50 patients excluded for this reason received >48 hours of mechanical ventilation. It is impossible to establish fully if this influenced the overall outcome of A2B, but in a pragmatic effectiveness trial likely represents 'real world' variation in clinical judgement which would be relevant to alpha2-agonist use in routine care. Issues such as this should be considered in future sedation research and clinical practice.¹⁹ In the A2B trial, the intervention was largely nurse-delivered at the patient bedside; despite this, nurse autonomy in tailoring sedation practice was not described by the participants during the interviews. Autonomy in practice relies on a clear understanding of nurses' appropriate role in sedation, strong inter-professional relationships, adequate education and support provided and a culture that fosters critical thinking, questioning and leadership.²⁰ Further exploration of the role of autonomy in practice, and how it supports or limits practice improvement, is warranted.

A lack of awareness of poorer patient outcomes associated with prolonged deep sedation was evident. The practice focus was not on proactively titrating and weaning sedation but centred around patient safety and deep sedation as a necessary means of maintaining patients and staff safety; staff shortages due to the COVID-19 pandemic may have exacerbated this. Implementing trial interventions that directly challenged embedded clinical practice through articulating a goal of lighter sedation was consequently challenging. This was amplified by a lack of staff familiarity with alpha-2 agents as first line sedatives and keeping patients lightly and comfortably sedated. To overcome this type of complex challenge, multidimensional change strategies that use a variety of different methods and address

change from multiple perspectives are needed in future similar studies. The challenges associated with complex or time-consuming documentation should also be noted, and abbreviated wherever possible.

While education is an essential component of behaviour change, it is rarely sufficient in isolation to produce sustained change, particularly in a complex environment.²¹ In the context of A2B, education to increase the knowledge and awareness of the impact of deep and protracted sedation on long term patient outcomes was described as beneficial for some clinicians. Additional elements to target identified in the A2B process evaluation include beliefs about consequences or impact of care, perceived roles in the health care team, social influences from other members of the health care team and resourcing, particularly numbers and experience of clinical staff.²²

Two core challenges presented during the A2B trial related to the COVID-19 pandemic. The first related to staff capabilities for delivering the intervention. Due to pressures on staff many senior and experienced staff left critical care. There were high staff turnover rates and an influx of new and inexperienced staff. Many nurses were also redeployed to critical care and, although experienced in other specialties, had not nursed in this environment before. Consequently, these staff had little or no experience of i) sedation management, and ii) alpha-2 agonist use. They required extensive support to deliver the study, particularly in the early stages, and adherence was compromised when that support was often removed out of hours. Second, COVID-19 patients were commonly much more deeply sedated than would have been routine pre-pandemic.²³ This meant that staff new to critical care perceived this as normal practice. There was crossover of this deep sedation practice into non-COVID-19 patients and a continuation into usual practice post-pandemic.

In contrast to the negative impacts and challenges, many clinical and research staff discussed the upside of conducting research during the pandemic. Whilst most research in critical care was paused, COVID-19 trials were expedited. Trial findings were rapidly published, and evidence-based interventions implemented into clinical practice. Many clinical staff discussed how this raised the profile of research on their units. They felt that the rapid process meant clinical staff who had delivered trials were more engaged because they got to see how effective interventions are implemented into real world practice. They contrasted this to the often-lengthy timeline of trials they typically deliver which can take years from conception to publication and implementation. As a result, many clinical and research staff felt the pandemic research process actually improved research culture and engagement.

The strengths of this process evaluation include that it was conducted across the duration of the A2B trial, with participation from personnel in a random selection of trial sites. A mixed methods approach

underpinned by a validated framework and pre-defined logic model was used, and all qualitative data collection and analysis was completed prior to knowing the primary results of the trial. Despite the strengths, there are also limitations associated with this process evaluation. Due to the implications of the COVID-19 pandemic, the majority of data collection occurred remotely through video-conferencing, rather than with observations and interviews conducted in situ – this possibly limited the depth of some data, but had the added benefit of broadening the number of potential participants as interviews could be conducted on multiple days. A further limitation is that the measures of intervention fidelity may not fully capture the complexity of the intervention, the differences between sites and the individual preferences or willingness to engage in the aims of the intervention – in this case to reduce propofol. Alternative measures of intervention fidelity may prove more appropriate. These quantitative data may also be compromised as a result of how the data were collected, for example different sites recorded eligible patients onto the recruitment log at different points in the screening process – therefore influencing the recorded rate of recruitment of eligible patients.

CONCLUSION

The majority of ICUs participating in the A2B trial adhered to the study protocol and delivered the intervention broadly as intended as measured through quantitative measures of fidelity. Despite this, interviews during this process evaluation revealed multiple contextual factors at the ICU and individual staff and patient level that prompted local adaption in specific circumstances. These contextual factors captured both organisational and human characteristics and represented the complexity of real world ICU practice that needs to be considered in both clinical trials and routine care. In the A2B trial these factors were exacerbated by the challenging context of the COVID-19 pandemic.

The focus on priorities in care were on short term safety and comfort – this was frequently attributed to staffing capacity and capability and a clear understanding of the potential safety consequences if sedation was too light for the patient. In contrast, the detrimental consequences of deeper sedation on recovery and rehabilitation were not so apparent, and therefore received less attention. Improvements in ICU sedation practice should be a priority of intensive care and require recognition of both short and long-term consequences of care in the context of a resource constrained environment.

Disclosure of conflicts of interest

The following conflicts of interest are declared:

- Bronagh Blackwood - Grant from NIHR Health Technology Assessment Agency; Ref NIHR164012 Paediatric Intensive Care Adaptive Platform Trial (PIVOTAL)
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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration.

Access to anonymised data may be granted following review.

Ethics statement

The A2B trial received ethical approval (21/08/2018) from the Scotland A REC (18/SS/0085); the protocol evaluation was included as a component of this approval.

Information Governance statement

The University of Edinburgh and NHS Lothian (Co-sponsors) are committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679.

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exercise your individual rights and the contact details for our Data Protection Officer here (<https://data-protection.ed.ac.uk/contact>). The University of Edinburgh is also the Data Processor

REFERENCES

1. Jackson DL, Proudfoot CW, Cann KF, Walsh T. A systematic review of the impact of sedation practice in the ICU on resource use, costs and patient safety. *Crit Care* 2010;**14**:R59.
2. Parker AM, Sricharoenchai T, Raparla S, Schneck KW, Bienvenu OJ, Needham DM. Posttraumatic stress disorder in critical illness survivors: a metaanalysis. *Crit Care Med* 2015;**43**:1121-9. <https://doi.org/10.1097/ccm.0000000000000882>
3. Olsen HT, Nedergaard HK, Strøm T, Oxlund J, Wian KA, Ytrebø LM, et al. Nonsedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients. *N Engl J Med* 2020;**382**:1103-11. <https://doi.org/10.1056/NEJMoa1906759>
4. Walsh TS, Aitken LM, McKenzie CA, Boyd J, Macdonald A, Giddings A, et al. Alpha 2 agonists for sedation to produce better outcomes from critical illness (A2B Trial): protocol for a multicentre phase 3 pragmatic clinical and cost-effectiveness randomised trial in the UK. *BMJ open* 2023;**13**:e078645. <https://doi.org/10.1136/bmjopen-2023-078645>
5. Eadie R, McKenzie C, Emerson L, Blackwood B, Aitken L, Hope D, et al. Clinical pharmacist's views on the role of alpha-2- agonists in practice and research for the management of agitation, sedation, and delirium (ASD). *Journal of the Intensive Care Society* 2022;**23**:1-210. <https://doi.org/10.1177/17511437221095122>
6. Nguyen V, Tiemann D, Park E, Salehi A. Alpha-2 Agonists. *Anesthesiol Clin* 2017;**35**:233-45. <https://doi.org/10.1016/j.anclin.2017.01.009>
7. Shehabi Y, Howe BD, Bellomo R, Arabi YM, Bailey M, Bass FE, et al. Early Sedation with Dexmedetomidine in Critically Ill Patients. *N Engl J Med* 2019;**380**:2506-17. <https://doi.org/10.1056/NEJMoa1904710>
8. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ* 2015;**350**:h1258. <https://doi.org/10.1136/bmj.h1258>
9. Aitken LM, Emerson LM, Kydonaki K, Blackwood B, Creagh-Brown B, Lone NI, et al. Alpha 2 agonists for sedation to produce better outcomes from critical illness (A2B trial): protocol for a mixed-methods process evaluation of a randomised controlled trial. *BMJ open* 2024;**14**:e081637. <https://doi.org/10.1136/bmjopen-2023-081637>
10. Walsh TS, Parker RA, Aitken LM, McKenzie CA, Emerson L, Boyd J, et al. Dexmedetomidine- or Clonidine-Based Sedation Compared With Propofol in Critically Ill Patients: The A2B Randomized Clinical Trial. *JAMA* 2025; 10.1001/jama.2025.7200. <https://doi.org/10.1001/jama.2025.7200>
11. Furber C. Framework analysis: a method for analysing qualitative data. *African Journal of Midwifery and Women's Health* 2010;**4**:97-100. <https://doi.org/10.12968/ajmw.2010.4.2.47612>
12. Shehabi Y, Serpa Neto A, Howe BD, Bellomo R, Arabi YM, Bailey M, et al. Early sedation with dexmedetomidine in ventilated critically ill patients and heterogeneity of treatment effect in the SPICE III randomised controlled trial. *Intensive Care Med* 2021;**47**:455-66. <https://doi.org/10.1007/s00134-021-06356-8>
13. McNett M, O'Mathúna D, Tucker S, Roberts H, Mion LC, Balas MC. A Scoping Review of Implementation Science in Adult Critical Care Settings. *Crit Care Explor* 2020;**2**:e0301. <https://doi.org/10.1097/cce.0000000000000301>
14. Beer M, Nohria N. Cracking the code of change. *Harv Bus Rev* 2000;**78**:133-41, 216.

15. Burnes B. Emergent change and planned change – competitors or allies? *International Journal of Operations & Production Management* 2004;**24**:886-902. <https://doi.org/10.1108/01443570410552108>
16. Pattison N, Arulkumaran N, Humphreys S, Walsh T. Exploring obstacles to critical care trials in the UK: A qualitative investigation. *J Intensive Care Soc* 2017;**18**:36-46. <https://doi.org/10.1177/1751143716663749>
17. European Medicines Agency. *Dexdor - direct healthcare professional communication(DHPC)*.2022.URL: <https://www.ema.europa.eu/en/medicines/dhpc/dexdor> (last accessed 15/11/24).
18. Shehabi Y, Serpa Neto A, Bellomo R, Howe BD, Arabi YM, Bailey M, et al. Dexmedetomidine and Propofol Sedation in Critically Ill Patients and Dose-associated 90-Day Mortality: A Secondary Cohort Analysis of a Randomized Controlled Trial (SPICE III). *Am J Respir Crit Care Med* 2023;**207**:876-86. <https://doi.org/10.1164/rccm.202206-1208OC>
19. Kristensen N, Nymann C, Konradsen H. Implementing research results in clinical practice- the experiences of healthcare professionals. *BMC Health Serv Res* 2016;**16**:48. <https://doi.org/10.1186/s12913-016-1292-y>
20. Gottlieb LN, Gottlieb B, Bitzas V. Creating Empowering Conditions for Nurses with Workplace Autonomy and Agency: How Healthcare Leaders Could Be Guided by Strengths-Based Nursing and Healthcare Leadership (SBNH-L). *J Healthc Leadersh* 2021;**13**:169-81. <https://doi.org/10.2147/jhl.S221141>
21. Arlinghaus KR, Johnston CA. Advocating for Behavior Change With Education. *Am J Lifestyle Med* 2018;**12**:113-6. <https://doi.org/10.1177/1559827617745479>
22. Atkins L, Francis J, Islam R, O'Connor D, Patey A, Ivers N, et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. *Implementation Science* 2017;**12**:77. <https://doi.org/10.1186/s13012-017-0605-9>
23. Balakrishna A, Walsh EC, Hamidi A, Berg S, Austin D, Pino RM, et al. An examination of sedation requirements and practices for mechanically ventilated critically ill patients with COVID-19. *Am J Health Syst Pharm* 2021;**78**:1952-61. <https://doi.org/10.1093/ajhp/zxab202>

Supplementary materials 1

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Supplementary File 2: Measures of intervention fidelity in the A2B trial

Site	Number of patients included in A2B analysis*	Score for fidelity: correct treatment administered	Score for fidelity: RASS -2 or lighter achieved	Score for dose: RASS recorded at least once per day	Score for reach: proportion of eligible patients randomised‡	RAG Total score	Categorisation of RAG Total score
1	1	0	3	3	0	6	Lowest adherence (6-7)
2	1	3	3	3	3	12	High adherence (10-12)
3	3	3	3	2	2	10	High adherence (10-12)
4	6	3	2	3	1	9	Moderate adherence (8-9)
5	6	3	3	3	0	9	Moderate adherence (8-9)
6	8	2	1	3	0	6	Lowest adherence (6-7)
7	8	2	2	3	0	7	Lowest adherence (6-7)
8	8	3	3	3	3	12	High adherence (10-12)
9	9	2	3	2	0	7	Lowest adherence (6-7)
10	12	3	3	3	3	12	High adherence (10-12)
11	14	3	3	3	2	11	High adherence (10-12)

Site	Number of patients included in A2B analysis*	Score for fidelity: correct treatment administered	Score for fidelity: RASS -2 or lighter achieved	Score for dose: RASS recorded at least once per day	Score for reach: proportion of eligible patients randomised‡	RAG Total score	Categorisation of RAG Total score
12	16	3	3	3	2	11	High adherence (10-12)
13	18	2	3	3	0	8	Moderate adherence (8-9)
14	19	2	3	3	2	10	High adherence (10-12)
15	20	2	3	3	0	8	Moderate adherence (8-9)
16	20	2	2	3	1	8	Moderate adherence (8-9)
17	21	3	3	3	2	11	High adherence (10-12)
18	22	3	2	3	2	10	High adherence (10-12)
19	25	3	3	3	2	11	High adherence (10-12)
20	29	3	2	3	1	9	Moderate adherence (8-9)
21	30	3	2	3	1	9	Moderate adherence (8-9)
22	30	2	3	3	0	8	Moderate adherence (8-9)
23	30	2	3	3	0	8	Moderate adherence (8-9)

Site	Number of patients included in A2B analysis*	Score for fidelity: correct treatment administered	Score for fidelity: RASS -2 or lighter achieved	Score for dose: RASS recorded at least once per day	Score for reach: proportion of eligible patients randomised‡	RAG Total score	Categorisation of RAG Total score
24	30	3	2	3	1	9	Moderate adherence (8-9)
25	33	3	3	3	0	9	Moderate adherence (8-9)
26	33	2	3	3	0	8	Moderate adherence (8-9)
27	36	3	3	3	2	11	High adherence (10-12)
28	37	3	3	3	0	9	Moderate adherence (8-9)
29	38	3	3	3	0	9	Moderate adherence (8-9)
30	47	3	3	3	1	10	High adherence (10-12)
31	59	2	2	3	3	10	High adherence (10-12)
32	63	2	3	3	0	8	Moderate adherence (8-9)
33	65	2	3	3	0	8	Moderate adherence (8-9)
34	67	3	2	3	1	9	Moderate adherence (8-9)
35	77	3	2	3	2	10	High adherence (10-12)

Site	Number of patients included in A2B analysis*	Score for fidelity: correct treatment administered	Score for fidelity: RASS -2 or lighter achieved	Score for dose: RASS recorded at least once per day	Score for reach: proportion of eligible patients randomised‡	RAG Total score	Categorisation of RAG Total score
36	89	3	2	3	1	9	Moderate adherence (8-9)
37	96	3	3	3	0	9	Moderate adherence (8-9)
38	146	2	3	3	1	9	Moderate adherence (8-9)

*Includes all patients in the analysis population and recorded as being on ventilation for at least part of the follow-up period.

‡ All randomised patients included – even those excluded from the A2B analysis population.

Supplementary Materials 3: Themes and quotes

Themes	Sub-themes	Quotes
Participant related factors	Clinician preference	<ul style="list-style-type: none"> <li data-bbox="913 316 2045 507">• <i>I don't think between the arms, no. Because they're medications people already use, I think it's been very straightforward and everyone feels quite confident with all three arms and titrating them according to the patient, like they would do with Propofol and remi, I think. ResN03/15</i> <li data-bbox="913 531 2045 671">• <i>...they're probably happier with clonidine. But you just get less bradycardia with it and...even though that might end up being an important result. So that's...it's definitely been the dex arm that's been the most challenging, I think... PI06/11</i> <li data-bbox="913 695 2045 1102">• <i>...it was a bit harder to stop the addition of Dexdor or Clonidine in those people randomised to Propofol... But I suspect there were some instances where it wasn't that clinicians were deliberately violating the protocol, but I think they probably just forgot and slipped back into usual practice. So those patients who are agitated, we want to extubate them, let's put them on some Dexdor, and then you suddenly go ah, that's a protocol deviation because we're on the Propofol arm. Whereas I think once you knew oh, the patient's in A2B, they've already had Clonidine, because you know that you know you don't give Dexdor I think that was a bit more obvious. PI01/26</i> <li data-bbox="913 1126 2045 1318">• <i>I think the only danger with the propofol is that actually the...there's just a tendency and a global tendency to over sedate patients. And, you know, I think on the treatment arms if you like, maybe there's a little bit more focus. But sometimes on the propofol arm, it's easy just to sit back and almost, you know, usual care, actually being over sedated. That's just a,</i>

		<p><i>sort of, side effect almost of the fact that people are doing what they normally do, if you see what I mean, on the propofol side, rather than trying to hit the RASS. PI05/19</i></p>
	Equipoise	<ul style="list-style-type: none"> • <i>...you get to the point that some people, sort of, said to the nurses, oh I'm not sure I'm equipoised to this trial anymore... But you know, they perceive that they already know the answer when they don't, you know, there is a little bit of that that comes across. PI03/32</i> • <i>...it was a consultant who's actually on the delegation log, who would say, he didn't have equipoise. Or there was a couple of occasions, like there was one recently, where the person was on Clonidine, and the consultant, he's very happy-go-lucky, but you know, he's very good, but he was like, well you can randomise them, but I'm going to put them on Clonidine, you know, irrespective, you know, I'll stop it and then I'll restart. And I said, well you don't have equipoise then, so we shouldn't put the patient on the trial. ResN07/30</i> • <i>...we have to tell them, you know, we can't choose, it's randomised by computer, so they could go into Propofol, Clonidine or Dexmedetomidine, and they're like, oh if there's a risk they're in Dex, absolutely not, you know? ResN05/02</i>
	Clinician resistance	<ul style="list-style-type: none"> • <i>...they're set in their ways, they want to keep them on Propofol and Alfentanil. So, there would be a portion of patients who also weren't recruited just because the consultant refused, even though they were eligible, so...they don't necessarily even have to give a reason, they just say, no. They've got the clinical command for the week, even though we're trying to highlight it and push it through. PI08/23</i> • <i>...we'd like to think of ourselves as a research active unit and everybody probably would say that they support research generally. But when it came to this trial, there are definitely one</i>

		<p><i>or two people that did not like it. And might try to avoid being asked to consent patients in to it and/or support it. PI05/19</i></p> <ul style="list-style-type: none"> <i>• My consultants are a bit of a mixed bunch unfortunately. Very keen...very keen to join the research, but when it gets to the practicalities, even some of those that are very research enthusiastic vocally, when it comes down to the individual patient, often it's very chaotic and it seems to them as though it will give a lot of extra work. Where actually it doesn't, because the research team and [research nurse] do the vast majority of it. So, that's partly dynamics within our unit, which is ongoing and challenging. PI10/17</i> <i>• You'd find some weeks, consultants who were on, everyone were going to A2B, and some weeks, none would go in. So, that's just consultant opinion on, potentially, their opinion on research, and whether they think they go in... Some of my colleagues would probably recruit no one into the trial, whereas other weeks, you'd get three or four. PI08/23</i> <i>• I don't think it's as...well I...obviously the normal care arm isn't an issue. I think it's either of the other arms. The...just the feeling that they're perhaps not as in...I'd say 'control', that's the wrong word but, you know, don't have the same confidence in the sedation and how it will perform I guess. PI05/19</i>
	<p>Staff capability and capacity</p>	<ul style="list-style-type: none"> <i>• Yeah, I'd say probably the less experienced nurses probably did struggle with it a bit more, because they would probably be less familiar with Dexdor or Clonidine. They are drugs that we use and we do use them as infusions but not obviously as frequently as Propofol. So, I think we're probably quite good at recognising who's going to need a little bit of extra help or teaching at the bedside. ResN06/32</i>

		<ul style="list-style-type: none">• <i>...in this case I think it was definitely because of the clinical experience the nurse had. They were very comfortable with the drugs, they were very comfortable weaning and assessing the patient. So they were comfortable. Whereas if you've got a junior band five who's absolutely terrified on a daily basis at the bedside and they haven't quite developed the skills to be comfortable in changing medication like an experienced band six would be. PI01/26</i>• <i>"Like the more experienced you are, the more confident in it, I suppose. And the more exposure you've had to sedated patients as a whole, then the more confident you are with your sedation, I suppose." RN01/15</i>• <i>I think the more senior nurses were probably more confident. I mean, like, the weaning and actually trying to maintain that RASS score balance. Whereas the junior staff I think were a bit more... I don't know what I'm doing, you know, am I... And, you know, you'd go down and they'd still be on the same amount of propofol as they were, like, two days ago, and you'd be, like, you can wean it down and wean this up and... You know, for the more junior staff it did take a little bit of time to get them confident. ResN20/17</i>• <i>I think for newer staff, it's difficult to say you don't know things, it's difficult to say you might need a hand with something. And yeah, it's absolutely terrifying environment to be nursing in and if you change the sedation and that person suddenly gets out of bed, then, you know, that's the nightmare scenario and that's very real in folks' minds. If I change...if I start tinkering with sedation, this person sits up and pulls a tube out, then we've got a whole world of problems, so... If it goes wrong, the stakes are high I think is what I'm getting at, the stakes are high so people are obviously cautious. ResN16/04</i>
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		<ul style="list-style-type: none">• <i>...you would see things like very high propofol, very low fentanyl and you would be like...you can...I don't know, I would kind of feel like the managing of the sedation wasn't great after COVID. And also because they would use more...as...more deep sedation so...yeah, I did really notice a change. And I'm...probably it's a mixture between what we did in COVID and a mixture of there is very new people and also very, very different backgrounds. ResN19/27</i>• <i>We'd go, oh, they're on midazolam already, why are they on midazolam, do they need to be on midazolam. You know, that's...I think it's been, you know, as you say practice... You know, we've been so used to keeping patients heavily sedated for COVID that it's trying to get out the other side of actually that practice and getting back to...you know, getting them so they're awake a bit more and interactive and able to wean. ResN20/17</i>• <i>I think it...it's just the confidence of the nurses at the bedside to wean the drugs at the right time...you know, the right rates and titrate the sedation to the target RASS... And I think that's just about that confidence, sort of, where...sort of, whether the patients going to suddenly erupt off the bed or not" PI05/19</i>• <i>As you know research nurses are the actual linchpins in the process. PI09/27</i>• <i>"...we've had a lot of new starters recently and I think it would just be too much to train every...all the bedside nurses up on the study all at once. So, we've just been doing...educating the nurse that's looking after the patient at the time. We're on the unit all the time, so up and down to the bedside a few times a day usually. And we're always available for them to phone us and get in touch and ask questions. But, yeah, I think just because of the proportion of new staff, it's just been mainly bedside teaching." ResN06/32</i>
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A2B trial-related factors	Concerns relating to safety and side effects	<ul style="list-style-type: none"> • <i>There was a lot of fear round the...tended only to be around the Dexdor, even though it happened, yes, with clonidine, it tended only to be with the Dexdor, oh but he is bradycardic, or, you can't put him on, his heart rate's only 60... ResN14/38</i> • <i>I wouldn't be feeling that I'd want to switch to using dexmedetomidine as a first-line sedative agent in all patients by any means, I think. It's, you know, it does have some other issues the bradycardia and asystole, you know, we've known about during the trial. Yeah, that would certainly put me of, I think, using it as a first-line sedative agent. P103/32</i> • <i>...you would say to them, you know, why...you know, why did we not do this there, you know, and they always...it's always patient safety overnight, I think a lot of them would give you that, you know, say, but he was agitated through...there's less people around and it's...patient safety would always be brought up as a thing of, but we didn't do it because...to keep the patient safe and agitation. ResN14/38</i> • <i>And you know the moment a patient...if they wake up with delirium and you've got next to you a junior nurse that has gone in to this freeze mode because the patient woke up, you're basically on your own. So you just start thinking about safety rather than, can I actually...you need to think if you're actually going to wake up that patient in a safe way, and they're not going to pull the tube or anything. ResN19/27</i>

		<ul style="list-style-type: none"> • <i>...say someone they felt had a... was prone to some bradyarrhythmia, or maybe even who'd just had a laparotomy and was going to be in an ileus, they'd say, well, we're not going to give this person Clonidine, because it's just going to make their ileus worse... But it wouldn't bother me, I would give it a go, because I still think...the other medications we give people, notably Alfentanil in massive doses, also causes ileus in people, so it's difficult to pick them apart, realistically. And being extubated on Clonidine, to me, is much better than being intubated on a whacking dose of Alfentanil... PI08/23</i> • <i>I would be reluctant to do that on the basis of the information that, obviously you know, we were kept updated by the trial coordinators... because we were part of the trial, you know, Tim and the team kept us more up to date with the interpretation of the SPICE III trial it's, perhaps, more in the front of our minds than it would have been otherwise" PI03/32</i>
	Overnight deep sedation practice	<ul style="list-style-type: none"> • <i>Because it can go from, like, nought to a hundred very quickly, so I think it's that fear of someone suddenly waking, has made people worry. RN02/32</i> • <i>I think there is a bit of a recognition that that practice slips over into our other patients, and I don't think as a consultant body we're as good at, say, setting RASS targets as we are at setting, say, blood pressure targets... and also, as [Research Nurse] says, coming out of COVID where we had to keep a lot of the patients deep for safety... it may be that being part of A2B has helped a little bit with that and really made us think about sedation practices. PI01/26</i> • <i>But, you know, staff have to get used to patients being awake with a breathing tube, again. You know, for years, it was abnormal to have patients deeply sedated, because we've gone past that." ResN07/30</i>

		<ul style="list-style-type: none"> • <i>You see, now we're using double the dose of Fentanyl to what we used pre-COVID, which is so interesting... Because it's just what they got used to. ResN07/30</i>
	Patient comfort	<ul style="list-style-type: none"> • <i>I don't think we've had any particular feedback about the people who were on Dexdor or Clonidine were more or less in discomfort or pain, our usual patients. I think that's probably because we would usually put people on an opiate and remifentanyl. So it's probably a little bit difficult to unpick. PI01/26</i> • <i>I think the, sort of...of...the alpha-2 agonist effects on pain is quite often not that well understood, you know, by some of the staff...if that answers the question. So there's guidelines in place but it's...you know, not everybody is a hundred per cent on it. PI09/27</i> • <i>I think the pain management thing is interesting, because alpha2-agonists, we've got the analgesic side of it as well. Which I try and always get the Fentanyl down on patients, but people do tend to keep, like, Dex and Fen, or Clonidine and Fen. And I have the conversation that they don't necessarily need them as much. ResN08/30</i> • <i>I think the ones it tends to work well, from my...just, sort of, anecdotally, are those that have a higher alcohol intake when they're coming in. Or have previous opiate high intake or recreational drug use. I think that's one cohort that it works particularly well in, or they work particularly well in. PI10/17</i> • <i>...we usually find people that have had...drink quite a lot of alcohol, use recreational drugs, are difficult to sedate. And already the nurses have got, sort of like, a fear of the patients waking up, extubating themselves. So I feel like a lot of our patients have other problems, so it is quite a difficult trial to run. Obviously if they were all easy to sedate, woke up okay,</i>

		<p><i>that would be the ideal world and we wouldn't need to do this trial. But I feel like that probably has been one of the issues with the nurses. ResN10/19</i></p> <ul style="list-style-type: none"> • <i>I don't know if it's because if they were agitated before they went to sleep, they're still agitated. I suppose whatever has happened is still ongoing. And then they just seem to need the higher levels of sedation and you can't always chip away at the propofol quite as much as you can on others. RN01/15</i> • <i>And I do think, Clonidine and Dex do facilitate just like, a nicer plateaued, consistent level of sedation... Whereas, I'd say generally speaking with Propofol, you're either flat, or you're actually quite uncomfortable. Whereas, I think Dex, and Clonidine, I do feel that you do just get a nicer continuum of sedation, that looks comfortable. ResN08/30</i> • <i>...my impression would be that they tend to be a little bit more awake [on alpha-2 agonists]...potentially. I don't...I haven't equated that to having increased pain or increased discomfort per se. P105/19</i>
	Trial documents	<ul style="list-style-type: none"> • <i>Yeah, you know the flowchart and then on the reverse of that there's what to do if x, y, and z happens, some folk were really relieved to have that information, they felt that was important and they wanted it and it was useful to them and they referred to it. ResN16/04</i> • <i>...the bedside packs are helpful. People go to those quite a lot for information. And if they don't get the answers there, they've got us to go to. We're here Monday to Friday...we all work on weekends as bank shift, so we're always here really if they've got any questions. ResN04/15</i> • <i>...a lot of people when we talked to them, it was, like, well, actually it [trial shift form] wasn't a high consideration and priority on my part because, you know, I've got eight infusions and</i>

		<p><i>a filter going on. And, you know, to stop and just tick a RASS score and fill in a quick questionnaire, you know, we've had a busy 12-hour shift, it's sometimes the lowest thing on their priority. ResN20/17</i></p>
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