**Supplementary Materials 3: Themes and quotes**

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| **Themes** | **Sub-themes** | **Quotes** |
| Participant related factors | Clinician preference | * *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 * *…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 * *…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 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, 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 |
|  | Equipoise | * *…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 * *…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 * *…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 |
|  | Clinician resistance | * *…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 * *…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 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 * *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 * *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 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 |
|  | Staff capability and capacity | * *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 * *…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 * *“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 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 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 * *…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 * *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 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 * *As you know research nurses are the actual linchpins in the process.* PI09/27 * *“…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 think that more so than maybe any other trial that I think we’ve done, this one has so much reliance on the bedside staff and so much, kind of, look, the whole trial couldn't run without them. So it’s having that communication, education and…I’d have to say the fact that we have had such a hands on PI has made…you know, has made that process a lot easier.* ResN15/38 |
| A2B trial-related factors | Concerns relating to safety and side effects | * *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 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.* PI03/32 * *…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 * *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 * *…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 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 |
|  | Overnight deep sedation practice | * *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 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 * *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 * *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 |
|  | Patient comfort | * *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 remifentanil. So it’s probably a little bit difficult to unpick.* PI01/26 * *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 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 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 * *…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, 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 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 * *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 * *…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.* PI05/19 |
|  | Trial documents | * *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 * *…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 * *…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 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 |