A2B – a study investigating the effect of different types of sedation on the length of time critically ill patients require ventilation in intensive care

Submission date 23/10/2018	Recruitment status No longer recruiting	Prospectively registered[X] Protocol
Registration date 25/10/2018	Overall study status Completed	[X] Statistical analysis plan[X] Results
Last Edited 04/07/2025	Condition category Other	Individual participant data

Plain English summary of protocol

Background and study aims

Many patients in intensive care (ICU) need help to breathe on a breathing machine and need pain killers and sedatives to keep them comfortable and pain-free. However, keeping patients too deeply sedated can make their ICU stay longer, can cause ICU confusion (delirium), and afterwards may cause distressing memories. Ideally, we want to keep patients less sedated, but it is difficult to get the balance of sedation and comfort right. For sedation, most ICUs use a drug called propofol that is good at reducing anxiety and making people sleepy, but is not a painkiller, so additional painkillers are needed. There are two other drugs used less often called alpha-2 agonists that have both sedative and painkilling actions, which may make it easier for patients to be more awake and comfortable on the ventilator. The two drugs are called clonidine and dexmedetomidine. The aim of this study is to find out whether starting an alpha2-agonist drug early in ICU, and using this instead of propofol as much as possible, can help keep patients more lightly sedated but still comfortable, and whether patients spend less time on the ventilator with these drugs. The researchers also want to find out how safe they are, if they can improve important outcomes during ICU stay (like delirium, comfort, and safety) and during recovery (like bad memories, anxiety, and depression), and if they are value for money.

Who can participate?

Patients aged 18 years and over who need to be on a ventilator for at least 2 days

What does the study involve?

Patients are randomly allocated to one of three groups. One group continues to receive propofol, one group receives dexmedetomidine, and one group receives clonidine. All patients receive extra pain relief if needed, and patients in the dexmedetomidine and clonidine groups continue to receive propofol if they need this in addition. Nurses and doctors alter the doses of sedation drugs to try and reduce or stop them, but always aiming to have patients lightly sedated and comfortable. The study assesses whether patients on dexmedetomidine or clonidine come off the ventilator quicker than those just on propofol, and looks at whether

there is a difference between the groups in the number of people who experience delirium in ICU, how comfortable people are, and whether participants' memories of being in the ICU differed. Participants are followed up for 180 days afterwards to see if there are differences in the after-effects of being ill in ICU between the groups. Participants complete questionnaires to assess their memories of the ICU experience at 90 days after entering the trial. At 180 days, they also complete questionnaires about their quality of life or if they suffer from anxiety, depression or stress. Value for money is important because the costs of clonidine, dexmedetomidine, and propofol are quite different. Clonidine, in particular, is relatively inexpensive. ICU nurses' and doctors' views are collected on how easy or difficult it was to adjust and use the drugs, to provide valuable practical information that can be shared with other ICUs, particularly if alpha2-agonists are found to be better and other ICUs want to start using them. [Note that for participants recruited in the final months of trial recruitment, the 90- and 180-day follow-up will be truncated and not collected. This was agreed with the TSC and funder to reduce trial costs and enable trial completion.]

What are the possible benefits and risks of participating?

There are no direct benefits to taking part in the trial but it may help to improve outcomes for patients requiring treatment with a ventilator in ICU in the future. As the sedative drugs being used in this study are commonly used drugs, the potential risk to patients on the trial is similar to the potential risk of patients on ventilation and sedative therapy who are not in the trial.

Where is the study run from? The University of Edinburgh (UK)

When is the study starting and how long is it expected to run for? April 2018 to July 2024

Who is funding the study? The NIHR Health Technology Assessment Programme (UK)

Who is the main contact?

1. Sian Irvine, sian.irvine@ed.ac.uk

2. Prof. Timothy Walsh, timothy.walsh@ed.ac.uk

Study website

https://www.ed.ac.uk/usher/edinburgh-clinical-trials/our-studies/all-current-studies

Contact information

Type(s) Public

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Type(s)

Scientific

Contact name Prof Timothy Walsh

ORCID ID https://orcid.org/0000-0002-3590-8540

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Additional identifiers

EudraCT/CTIS number 2018-001650-98

IRAS number 243640

ClinicalTrials.gov number NCT03653832

Secondary identifying numbers HTA 16/93/01, IRAS 243640

Study information

Scientific Title

Alpha 2 agonists for sedation to produce better outcomes from critical illness (A2B Trial): a randomised, parallel-group, allocation concealed, controlled, open, Phase III pragmatic clinical and cost-effectiveness trial with internal pilot

Acronym

Study objectives

The primary hypothesis is that sedation with α2-agonists decreases the time to extubation in adult mechanically ventilated ICU patients compared with usual care.

Ethics approval required

Old ethics approval format

Ethics approval(s)

Approved 21/08/2018, Scotland A Research Ethics Committee (2nd Floor, Waverley Gate, 2-4 Waterloo Place, Edinburgh, EH1 3EG, United Kingdom; +44 (0)131 465 5680; manx. neill@nhslothian.scot.nhs.uk), ref: 18/SS/0085

Study design

Randomized, parallel-group, allocation concealed, controlled, open-label, phase III, pragmatic, clinical and cost-effectiveness multi-centre trial with an internal pilot

Primary study design

Interventional

Secondary study design

Randomised parallel trial

Study setting(s) Hospital

Study type(s)

Treatment

Participant information sheet

Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied

Critically ill intensive care patients receiving mechanical ventilation

Interventions

Patients will be allocated in a 1:1:1 ratio to the three trial groups detailed below using permuted blocks (randomly arranged sizes of 3, 6, 9, 12) stratified by centre using a remote web-based randomisation system:

1. Dexmedetomidine - dosing regimen - the regimen will follow the manufacturer's guidance and regimens used in previous trials. Dexmedetomidine will be up and down titrated against sedation targets set by clinical staff and reviewed at regular intervals, and documented at least daily. No loading dose will be administered. The starting dose will be 0.7 μg/kg/hour titrated to a maximum dose 1.4 μg/kg/hour. Lower starting doses will be used at clinical discretion for patients with cardiovascular instability.

2. Clonidine – dosing regimen is similar to that currently used in many UK ICUs as part of routine 'off label' practice. Clonidine will be up and down titrated against sedation targets set by clinical staff and reviewed at regular intervals, and at least daily. No loading dose will be administered. The starting dose will be 1.0 µg/kg/hour titrated to a maximum dose of 2.0 µg/kg/hour.

A2B

3. Propofol (usual care) – dosing regimen - participants will continue to receive intravenous propofol according to current usual care. The sedation targets, weaning, and sedation discontinuation procedures will follow the same clinical targets as for the clonidine and dexmedetomidine groups.

Patients will commence intravenous infusion of open-label study drug according to a weightbased dose regimen as early as possible post randomisation, and within a maximum of 2 h. Bedside clinical staff will transition patients to achieve sedation with the allocated a2-agonist agent as quickly as clinically feasible and safe, to replicate the way these drugs would be used in routine practice. Additional opiate will be used for analgesia using clinical judgement.

The intervention period will continue until the patient is weaned from MV and sedation in the ICU. The timing of discontinuation of sedative agents will be at the discretion of the clinical team.

Intervention Type

Drug

Phase

Phase III

Drug/device/biological/vaccine name(s)

Dexmedetomidine, clonidine, propofol

Primary outcome measure

Time to successful extubation post-randomisation (hours). A successful first extubation from mechanical ventilation will be defined as follows:

1. From endotracheal extubation: time of first extubation that is followed by 48 hours of spontaneous breathing

2. From tracheostomy: time of extubation will be defined as the first time a patient receives support not exceeding 5 cmH2O CPAP with less or equal to pressure support ventilation of 5cmH2O for a continuous period of 48 hours

Added 30/07/2024:

3. From non-invasive mechanical ventilation (NIV): time of extubation will be the start time of the first period during which a patient receives support not exceeding 5 cmH2O CPAP via mask /hood for a continuous period of 48 hours. NIV patients receiving any pressure-supported breaths will not be considered to be spontaneously breathing unassisted.

Timepoints: Time of randomisation and time of successful extubation

Secondary outcome measures

Current secondary outcome measures as of 09/03/2022:

 Length of ICU stay (number of days). ICU status will be recorded daily from the date of randomisation until the date of ICU discharge, or 180 days, whichever comes first
 Delirium during ICU stay, assessed twice daily during ICU stay using the Confusion-Agitation method for ICU (CAM-ICU). Delirium will be assessed from the date of randomisation until the date of ICU discharge, or 28 days, whichever comes first

3. Duration of delirium during ICU stay. Delirium will be assessed twice daily during ICU stay using the Confusion-Agitation method for ICU (CAM-ICU). Delirium will be assessed from the date of randomisation until the date of ICU discharge, or 28 days, whichever comes first 4. Sedation quality measured by Richmond Agitation and Sedation Scale (RASS) 4 hourly during the period of ventilation from the date of randomisation until the participant is successfully extubated, or 28 days, whichever comes first

5. Sedation quality measured by Sedation Quality Assessment Tool (SQAT) daily during the period of ventilation from the date of randomisation until the participant is successfully extubated, or 28 days, whichever comes first

6. Analgesia quality measured by Richmond Agitation and Sedation Scale (RASS) 4 hourly during the period of ventilation from the date of randomisation until the participant is successfully extubated, or 28 days, whichever comes first

7. Analgesia quality measured by Sedation Quality Assessment Tool (SQAT) daily during the period of ventilation from the date of randomisation until the participant is successfully extubated, or 28 days, whichever comes first

8. Number of hours to first optimum sedation as measured by a RASS score of -2 or greater. Level of sedation will be assessed 4 hourly during the period of ventilation from the date of randomisation until the participant is successfully extubated, or 28 days, whichever comes first 9. Number of days to first optimum sedation as assessed by the Sedation Quality Assessment Tool (SQAT). Level of sedation will be assessed daily during the period of ventilation from the date of randomisation until the participant is successfully extubated, or 28 days, whichever comes first

10. Ability to communicate pain. Binary assessment by bedside nurse twice daily during the period of ventilation from the date of randomisation until the participant is successfully extubated, or 28 days, whichever comes first

11. Ability to co-operate with care. Binary assessment by bedside nurse twice daily during the period of ventilation from the date of randomisation until the participant is successfully extubated, or 28 days, whichever comes first

12. Relative/Partner/Friend (PerLR) assessment of wakefulness. Response to verbal question, assessed by a Relative/Partner/Friend daily during the period of ventilation from the date of randomisation until the participant is successfully extubated, or 28 days, whichever comes first 13. Relative/Partner/Friend (PerLR) assessment of patient comfort. Response to verbal question, assessed by a Relative/Partner/Friend daily during the period of ventilation from the date of randomisation until the participant is successfully extubated, or 28 days, whichever comes first 14. Relative/Partner/Friend (PerLR) assessment of patient communication. Response to verbal question, assessed by a Relative/Partner/Friend daily during the period of ventilation from the date of randomisation until the participant is successfully extubated, or 28 days, whichever comes first 14. Relative/Partner/Friend (PerLR) assessment of patient communication. Response to verbal question, assessed by a Relative/Partner/Friend daily during the period of ventilation from the date of randomisation until the participant is successfully extubated, or 28 days, whichever comes first first first of randomisation until the participant is successfully extubated, or 28 days, whichever comes first date of randomisation until the participant is successfully extubated, or 28 days, whichever comes first f

15. Incidence of drug-related adverse events (bradycardia, hypotension, hypertension, cardiac arrhythmias, cardiac arrest) as documented in the medical records recorded daily from the date of randomisation until the date of documented successful extubation, or 28 days, whichever comes first

16. Incidence of mortality, as documented in the medical records from the date of randomisation until the date of the last follow-up visit at 180 days

17. Patient experience of ICU care measured by Intensive Care Experience Questionnaire at 90 days post ICU discharge

18. Occurrence of anxiety and depression measured by Hospital Anxiety and Depression Scale (HADS) questionnaire at 180 days post ICU discharge

19. Occurrence of post-traumatic stress measured by Impact of Events Scale-revised (IES-R) at 180 days post ICU discharge

20. Cognitive function assessed using the Montreal Cognitive Assessment Tool (Postal or Telephone) at 180 days post ICU discharge

21. Health-related quality of life (recalled) assessed by EuroQol tool (EQ-5D-5L) at 30 days post ICU discharge - recalled prior to hospital admission

22. Health-related quality of life (30 day) assessed by EuroQol tool (EQ-5D-5L) at 30 days post ICU discharge

23. Health-related quality of life (90 day) assessed by EuroQol tool (EQ-5D-5L) at 90 days post ICU discharge

24. Health-related quality of life (180 day) assessed by EuroQol tool (EQ-5D-5L) at 180 days post ICU discharge

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 Length of ICU stay (number of days). ICU status will be recorded daily from the date of randomisation until the date of ICU discharge, or 180 days, whichever comes first
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27. Health-related quality of life (90 day) assessed by EuroQol tool (EQ-5D-5L) at 90 days post ICU discharge

28. Health-related quality of life (180 day) assessed by EuroQol tool (EQ-5D-5L) at 180 days post ICU discharge

Overall study start date

01/04/2018

Completion date

31/07/2024

Eligibility

Key inclusion criteria

Current participant inclusion criteria as of 22/06/2020:

- 1. Patient requiring mechanical ventilation (MV) in an ICU
- 2. Aged 18 years or over
- 3. Within 48 h of first episode of MV in ICU
- 4. Requiring sedation with propofol
- 5. Expected to require a total of 48 hours of MV or more in ICU

6. Expected to require a further 24 hours of MV or more at the time of randomisation in the opinion of the responsible clinician

Previous inclusion criteria:

- 1. Patient requiring mechanical ventilation (MV) in an ICU
- 2. Aged 18 or over

3. Within 48 hours of starting MV in an ICU

4. Requiring sedation with propofol

5. Expected to require a total of 48 hours of MV or more in ICU

6. Expected to require a further 24 hours of MV or more at the time of randomisation in the opinion of the responsible clinician

Participant type(s)

Patient

Age group

Adult

Lower age limit

18 Years

Sex

Both

Target number of participants

1437

Total final enrolment

1437

Key exclusion criteria

Current exclusion criteria as of 22/06/2020:

1. Acute brain injury (traumatic brain injury; intracranial haemorrhage; ischaemic brain injury from stroke or hypoperfusion)

- 2. Post-cardiac arrest (where there is clinical concern about hypoxic brain injury)
- 3. Status epilepticus
- 4. Continuous therapeutic neuromuscular paralysis at the time of screening or randomisation
- 5. Guillain-Barre Syndrome
- 6. Myasthenia gravis
- 7. Home ventilation
- 8. Fulminant hepatic failure
- 9. Patient not expected to survive 24 h by responsible clinician
- 10. Decision to provide only palliative or end-of-life care
- 11. Pregnancy
- 12. Known allergy to one of the study drugs
- 13. Untreated second or third degree heart block
- 14. Transferred from another Intensive Care Unit in which MV occurred for >6 h
- 15. Prisoners
- 16. Enrolled on another CTIMP
- 17. Previously enrolled on the A2B Trial

18. Patients with bradycardia: a heart rate of <50 bpm for a period of 60 min or longer since starting MV in the ICU

Previous exclusion criteria:

1. Acute brain injury (traumatic brain injury; intracranial haemorrhage; ischaemic brain injury from stroke or hypoperfusion)

2. Post-cardiac arrest (where there is clinical concern about hypoxic brain injury)

- 3. Status epilepticus
- 4. Continuous therapeutic neuromuscular paralysis at the time of screening or randomisation
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- 17. Previously enrolled on the A2B Trial

Date of first enrolment

30/09/2018

Date of final enrolment

31/10/2023

Locations

Countries of recruitment England

Northern Ireland

Scotland

United Kingdom

Wales

Study participating centre NHS Lothian

The Royal Infirmary of Edinburgh 51 Little France Crescent Edinburgh United Kingdom EH16 4SA

Study participating centre Belfast Health and Social Care Trust Royal Victoria Hospital 274 Grosvenor Road Belfast United Kingdom BT12 6BA

Study participating centre Blackpool Teaching Hospitals NHS Foundation Trust Victoria Hospital Whinney Heys Road Blackpool United Kingdom FY3 8NR

Study participating centre Leeds Teaching Hospitals NHS Trust St James University Hospital Beckett Street Leeds United Kingdom LS9 7TF

Study participating centre St George's University Hospitals NHS Foundation Trust St George's Hospital Blackshaw Road Tooting London United Kingdom SW17 0QT

Study participating centre North Bristol NHS Trust Southmead Hospital Southmead Road Westbury-On Trym Bristol United Kingdom BS10 5NB

Study participating centre Poole Hospitals NHS Foundation Trust Poole Hospital Longfleet Road Poole United Kingdom BH15 2JB

Study participating centre King's College Hospital NHS Foundation Trust King's College Hospital Denmark Hill Brixton London United Kingdom SE5 9RS

Study participating centre Lewisham and Greenwich NHS Trust University Hospital Lewisham Lewisham High Street London United Kingdom SE13 6LH

Study participating centre West Hertfordshire Hospitals NHS Trust Watford General Hospital Vicarage Road Watford United Kingdom WD18 0HB

Study participating centre Cardiff and Vale University Health Board University Hospital of Wales Heath Park Cardiff United Kingdom CF14 4XW

Study participating centre NHS Greater Glasgow and Clyde Royal Alexandra Hospital Corsebar Road Paisley United Kingdom PA2 9PN

Study participating centre Countess of Chester Hospital NHS Foundation Trust Countess of Chester Hospital Liverpool Road Chester United Kingdom CH2 1UL

Study participating centre Cambridge University Hospitals NHS Foundation Trust Addenbrooke's Hospital Hills Road Cambridge United Kingdom CB2 0QQ

Study participating centre North Tees and Hartlepool NHS Foundation Trust University Hospital of Hartlepool Holdforth Road Hartlepool United Kingdom TS24 9AH

Study participating centre The Newcastle upon Tyne Hospitals NHS Foundation Trust Newcastle Freeman Hospital Freeman Road High Heaton Newcastle-upon-Tyne United Kingdom NE7 7DN

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Study participating centre Leicester Royal Infirmary

University Hospitals of Leicester NHS Trust Leicester United Kingdom LE1 5WW

Study participating centre John Radcliffe Hospital

Oxford University Hospitals NHS Foundation Trust Headley Way Oxford United Kingdom OX3 9DU

Study participating centre

Harrogate District Hospital Harrogate and District NHS Foundation Trust Lancaster Park Road Harrogate United Kingdom HG2 7SX

Study participating centre

Musgrove Park Hospital Taunton and Somerset NHS Foundation Trust Parkfield Road Taunton United Kingdom TA1 5DA

Study participating centre Manchester Royal Infirmary

Manchester University NHS Foundation Trust Oxford Road Manchester United Kingdom M13 9WL

Study participating centre

Heartlands Hospital University Hospitals Birmingham NHS Foundation Trust Bordesley Green East Birmingham United Kingdom B9 5SS

Study participating centre Queen Elizabeth Hospital

The Queen Elizabeth Hospital Kings Lynn NHS Foundation Trust Gayton Road Kings Lynn United Kingdom PE30 4ET

Study participating centre

Queens Medical Centre Nottingham University Hospitals NHS Trust Derby Road Nottingham United Kingdom NG7 2UH

Study participating centre

Medway Maritime Hospital

Medway NHS Foundation Trust Windmill Road Gillingham United Kingdom ME7 5NY

Study participating centre

University College Hospital University College London Hospitals NHS Foundation Trust 235 Euston Road London United Kingdom NW1 2BU

Study participating centre Russells Hall Hospital

The Dudley Group NHS Foundation Trust Dudley United Kingdom DY1 2HQ

Study participating centre Bristol Royal Infirmary

University Hospitals Bristol NHS Foundation Trust Bristol United Kingdom BS2 8HW

Study participating centre

Aintree University Hospital Aintree University Hospital Foundation Trust Lower Lane Liverpool United Kingdom L9 7AL

Study participating centre

Royal Gwent Hospital Aneurin Bevan University Health Board Cardiff Road Newport United Kingdom NP20 2UB

Study participating centre

Altnagelvin Area Hospital

Western Health and Social Care Trust Glenshane Road Londonderry United Kingdom BT47 6SB

Study participating centre

NHS Dumfries and Galloway Grierson House The Crichton Bankend Road Dumfries United Kingdom DG1 4ZG

Study participating centre Liverpool University Hospitals NHS Foundation Trust Royal Liverpool University Hospital Prescot Street Liverpool United Kingdom L7 8XP

Study participating centre Guy's & St Thomas Hospital Westminster Bridge Road London

United Kingdom SE1 7EH

Study participating centre South Eastern Health and Social Care Trust Trust Headquarters Ulster Hospital Upper Newtownards Road Dundonald Belfast United Kingdom BT16 1RH

Study participating centre Wye Valley NHS Trust County Hospital 27 Union Walk Hereford United Kingdom HR1 2ER

Study participating centre Western General Hospital Crewe Road South

Edinburgh Lothian United Kingdom EH4 2XU

Study participating centre Charing Cross Hospital Fulham Palace Road London United Kingdom W6 8RF

Study participating centre Hammersmith Hospitals NHS Trust Hammersmith Hospital Du Cane Road London

United Kingdom W12 0HS Study participating centre Belfast City Hospital

51 Lisburn Rd Belfast United Kingdom BT9 7AB

Study participating centre The Royal Victoria Infirmary Queen Victoria Road Newcastle upon Tyne United Kingdom TS1 4LP

Study participating centre Queen Elizabeth University Hospital 1345 Govan Road Glasgow United Kingdom G51 4TF

Sponsor information

Organisation Academic and Clinical Central Office for Research and Development (ACCORD)

Sponsor details

Research & Governance University of Edinburgh Queen's Medical Research Institute 47 Little France Crescent Edinburgh Scotland United Kingdom EH16 4TJ +44 (0)131 242 9418 enquiries@accord.scot

Sponsor type University/education

Website https://www.accord.scot/ ROR https://ror.org/01x6s1m65

Funder(s)

Funder type Government

Funder Name Health Technology Assessment Programme

Alternative Name(s) NIHR Health Technology Assessment Programme, HTA

Funding Body Type Government organisation

Funding Body Subtype National government

Location United Kingdom

Results and Publications

Publication and dissemination plan

The Clinical Study Report (CSR) will be submitted to the Sponsor and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The Chief Investigator will provide the CSR to ACCORD, for review, prior to finalization. The clinical study report may be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. The results of the study, together with other mandated information, will be uploaded to the European clinical trials database within 1 year of the end of the study. Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion). Please contact the study team for any further information or documentation (A2B@ed.ac.uk).

Intention to publish date

30/09/2024

Individual participant data (IPD) sharing plan

Current individual participant data (IPD) sharing statement as of 30/07/2024: The datasets generated during and/or analysed during the current study are/will be available upon request from Prof. Tim Walsh (Timothy.Walsh@ed.ac.uk). The data will not be available until around August 2024. Consent was requested from patients to anonymously share their data with other researchers.

Current individual participant data (IPD) sharing statement as of 09/03/2022: The datasets generated during and/or analysed during the current study are/will be available upon request from Prof. Tim Walsh (Timothy.Walsh@ed.ac.uk). The data will not be available until around June 2023. Consent was requested from patients to anonymously share their data with other researchers.

Previous individual participant data (IPD) sharing statement:

The datasets generated during and/or analysed during the current study are/will be available upon request from Prof. Tim Walsh (Timothy.Walsh@ed.ac.uk). The data will not be available until around August 2022. Consent was requested from patients to anonymously share their data with other researchers.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<u>HRA research summary</u>	version 7.0		28/06/2023	No	No
<u>Protocol article</u>		10/12/2023	30/07/2024	Yes	No
<u>Protocol file</u>		25/04/2023	30/07/2024	No	No
Statistical Analysis Plan		27/03/2024	30/07/2024	No	No
<u>Results article</u>		19/05/2025	04/07/2025	Yes	No