

Protocol and statistical analysis plan for the Randomised Evaluation of Active Control of Temperature versus Ordinary Temperature Management (REACTOR) trial

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Fever occurs commonly in patients in the intensive care unit and increases metabolic demand.^{1,2} Increases in metabolic demand have potentially deleterious physiological consequences, including increased oxygen consumption and cardiac output.² ICU patients with a range of critical illnesses, including trauma, infection, acute myocardial infarction and pancreatitis, develop fever.³⁻⁵ One potential method to reduce the physiological demands that ICU patients are subjected to is to systematically prevent and treat fever.⁶

Among patients without an infection, the presence of fever in the first 24 hours in the ICU is associated with an increased mortality risk, after adjustment for illness severity, which raises the possibility that an active approach to temperature control may be desirable in such patients.⁷ Mortality risk point estimates from ICU trials involving treatment of fever with paracetamol,⁸ ibuprofen⁹ and physical cooling¹⁰ typically favour the treatment strategy associated with the lowest body temperature. This is the case even among patients with infections (for whom the presence of fever in the first 24 hours after ICU admission is associated with a reduced mortality risk⁷). Despite this, in current practice, ICU clinicians are generally tolerant of a relatively high body temperature in ICU patients without acute brain injury,¹¹ which suggests that there is potential for a systematic approach to prevention and treatment of fever to reduce fever burden compared with standard care.

Existing evidence suggests that body temperature can be manipulated in ICU patients with medicines^{8,9} and physical cooling devices,¹⁰ but it is not known whether a systematic approach to prevention and treatment of fever can achieve lower mean body temperature than a standard-care approach. Understanding this is a prerequisite to evaluating such a temperature control strategy in a phase III clinical trial. If a systematic approach to temperature control does reduce mean body temperature, it is plausible that this approach might improve clinical outcomes for ICU patients with highly acute illnesses. This is because the adverse consequences of fever could be expected to outweigh any potential benefits for these patients.¹²

Here, we describe the study protocol and statistical analysis plan for the Randomised Evaluation of Active Control of Temperature versus Ordinary Temperature Management (REACTOR) trial.

ABSTRACT

Background: Body temperature can be reduced in febrile patients in the intensive care unit using medicines and physical cooling devices, but it is not known whether systematically preventing and treating fever reduces body temperature compared with standard care.

Objective: To describe the study protocol and statistical analysis plan for the Randomised Evaluation of Active Control of Temperature versus Ordinary Temperature Management (REACTOR) trial.

Design, setting and participants: Protocol for a phase II, multicentre trial to be conducted in Australian and New Zealand ICUs admitting adult patients. We will recruit 184 adults without acute brain injury who are expected to be ventilated in the ICU beyond the day after randomisation. We will use open, random, parallel assignment to systematic prevention and treatment of fever, or to standard temperature management.

Main outcome measures: The primary end point will be mean body temperature, calculated from body temperatures measured 6-hourly for 7 days (168 hours) or until ICU discharge, whichever is sooner. Secondary end points are ICU-free days, in-hospital and cause-specific mortality (censored at Day 90) and survival time to Day 90 (censored at hospital discharge).

Results and conclusions: The trial will determine whether active temperature control reduces body temperature compared with standard care. It is primarily being conducted to establish whether a phase III trial with a patient-centred end point of Day 90 mortality is justified and feasible.

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Aims

This phase II trial is principally being conducted to assess the feasibility of a subsequent phase III clinical trial. The proposed phase III trial will aim to answer the following question: among adults without acute brain injury who are expected to undergo ventilation in the ICU beyond the day after randomisation, does active control of body temperature alter Day 90 mortality compared with standard temperature management?

The primary aim of this trial is to establish the feasibility of testing an active temperature control strategy in a phase III trial, by determining whether or not it reduces mean body temperature compared with standard temperature management.

Methods

Trial design

The REACTOR trial is a multicentre, phase II, parallel-group, randomised controlled superiority trial including mechanically ventilated adults in the ICU without acute brain injury, who are expected to be ventilated beyond the day after randomisation. Participants will be allocated in a 1:1 ratio to active control of body temperature (intervention arm) or standard temperature management (control arm).

Setting and population

The trial will take place in Australian and New Zealand ICUs that admit adult patients.

Inclusion criteria

The inclusion criteria are:

- age 18 years or older
- requirement for invasive mechanical ventilation in the ICU and expected to be receiving it beyond the day after randomisation
- fever (defined as body temperature $\geq 37.8^{\circ}\text{C}$)¹³ in the previous 12 hours.

Exclusion criteria

The exclusion criteria are:

- acute brain injury (eg, traumatic brain injury, intracerebral haemorrhage, subarachnoid haemorrhage or ischaemic stroke)
- confirmed or suspected hypoxic ischaemic encephalopathy (including all patients who have had a recent cardiac arrest, for whom there is clinical concern about possible brain damage as a result)
- indication or contraindication for 6-hourly intravenous (IV) paracetamol 1 g, in the opinion of the treating clinician
- death is deemed to be inevitable as a result of the current acute illness, and either the treating clinician, the patient or the substitute decision maker is not committed to full active treatment

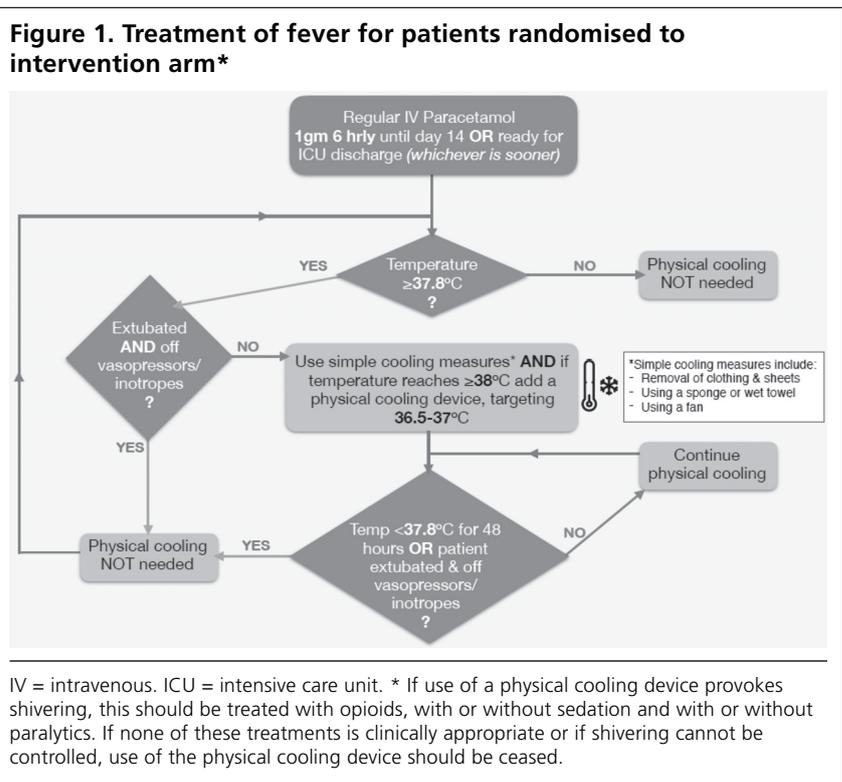
- a life expectancy of less than 90 days because of an underlying medical condition
- all other eligibility criteria fulfilled > 24 hours ago but patient was not enrolled in the study
- previous enrolment in the REACTOR study.

Study treatments

Intervention

The overarching goal for temperature management for patients allocated to the intervention group is to minimise fever, defined as a core body temperature $\geq 37.8^{\circ}\text{C}$,¹³ whenever possible. To attempt to achieve this aim, IV paracetamol 1 g will be administered every 6 hours from randomisation until the patient is ready to be discharged from the ICU, or reaches Day 14 after randomisation, or develops a contraindication to paracetamol. Between Day 14 and Day 28, paracetamol should be administered if the patient is febrile or can continue to receive it regularly, at the discretion of the treating clinician. If fever occurs after randomisation despite the use of paracetamol, it will be actively treated using physical cooling measures, beginning when the body temperature reaches 37.8°C (Figure 1).

When physical cooling is used, it will be discontinued when the temperature has been $< 37.8^{\circ}\text{C}$ for 48 hours, or sooner if the patient is extubated and no longer receiving inotropes and vasopressors. When physical cooling is discontinued, it will be reintroduced if fever recurs in a



patient requiring mechanical ventilation or inotrope or vasopressor support. All protocol-driven physical cooling will be discontinued at Day 28.

Shivering will be treated aggressively using the following hierarchy of treatments:

- 1 administration of an opioid bolus
- 2 increase in level of sedation
- 3 administration of a bolus of a neuromuscular blocking agent.

If treatments to control shivering are clinically inappropriate or shivering cannot be controlled, physical cooling may be discontinued.

Control

Temperature management of patients allocated to the control group will be at the discretion of the treating clinician. However, regular administration of paracetamol and use of IV paracetamol will both be discouraged unless there is a specific indication for one or both of these treatments.

Concomitant therapies

Temperature monitoring

Continuous monitoring of core body temperature will be used whenever possible, particularly while the patient is mechanically ventilated. When core temperature monitoring is considered clinically inappropriate, a tympanic

thermometer will be the preferred method for measuring temperature. In both study arms, temporal artery thermometers and axillary thermometers will not be used to monitor body temperature after enrolment, because of concerns about the accuracy of these devices.¹⁴

Fever investigation and treatment

In both treatment arms, the occurrence of a temperature $\geq 37.8^{\circ}\text{C}$ will trigger investigation for possible new infection and consideration of whether empirical therapy for new sepsis is required.

Outcome measures

Primary outcome measure

The primary outcome measure will be mean body temperature, calculated from the body temperature measurements 6-hourly for 7 days (168 hours) or until ICU discharge, whichever is sooner.

Secondary outcome measures

Secondary outcome measures will be:

- ICU-free days, defined as the number of days alive and outside the ICU, from randomisation until Day 28
- in-hospital mortality (censored at Day 90) and cause-specific mortality (reported as previously described¹⁵)
- survival time to Day 90 (censored at hospital discharge).

In addition, we will report a range of physiological outcomes (Table 1) and process-of-care measures (Table 2). The rate of recruitment (per site, per month) with 95% confidence intervals (CIs) will also be reported, with a view to planning a larger future trial. To reduce the risk of bias arising due to knowledge of the results emerging during the study analysis,¹⁶ the approach to presentation of study data has been pre-specified (Table 3).

Screening

All patients admitted to one of the study ICUs will be screened. Patients will be eligible for participation if they fulfil all inclusion criteria and none of the exclusion criteria. We will report patient flow data using an algorithm according to the Consolidated Standards of Reporting Trials (CONSORT) recommendations¹⁷ (Figure 2).

Randomisation

We will use a permuted block randomisation method with variable block sizes, stratified by site. Central randomisation will be performed using a secure, web-based, randomisation interface. Randomisation will be performed when participants fulfil all eligibility criteria and are ready to be assigned to study treatment. The allocation sequence will be generated by the study statistician, using computer-

Table 1. Physiological outcome measures

- Body temperature, measured 6-hourly for 7 days (168 hours) or until ICU discharge (whichever is sooner)
- Highest daily temperature after randomisation until ICU discharge or Day 28 (whichever is sooner)
- Proportion of patients with a post-randomisation body temperature in the ICU of $\geq 38.3^{\circ}\text{C}$ (censored at Day 28)
- Proportion of patients with a post-randomisation body temperature in the ICU of $\geq 39^{\circ}\text{C}$ (censored at Day 28)
- Heart rate, measured 6-hourly for 7 days (168 hours) or until ICU discharge (whichever is sooner)
- Respiratory rate, measured 6-hourly for 7 days (168 hours) or until ICU discharge (whichever is sooner)
- Mean arterial pressure, measured 6-hourly for 7 days (168 hours) or until ICU discharge (whichever is sooner)
- Highest recorded AST, ALT, ALP, GGT and bilirubin levels occurring between randomisation and ICU discharge (censored at Day 28)
- Highest serum creatinine level occurring between randomisation and ICU discharge (censored at Day 28)

ICU = intensive care unit. AST = aspartate aminotransferase.
ALT = alanine aminotransferase. ALP = alkaline phosphatase.
GGT = gamma-glutamyltransferase.

Table 2. Process-of-care measures

- ICU length of stay (overall and for survivors and non-survivors separately) (censored at Day 28)
- Hospital length of stay (overall and for survivors and non-survivors separately) (censored at Day 28)
- Ventilator-free days, to Day 28
- Vasopressor-free days, to Day 28
- Proportion of patients receiving new post-randomisation renal replacement therapy in the ICU (censored at Day 28)
- Days receiving IV antibiotics in the ICU (censored at Day 28)
- Number of sets of blood cultures performed in the ICU (censored at Day 28)
- Mean daily dose of paracetamol (until Day 28 or ICU discharge)
- Proportion of paracetamol doses administered via the IV route (until Day 28 or ICU discharge)
- Proportion of patients cooled with a physical cooling device (until Day 28 or ICU discharge)
- Duration of cooling therapy with a physical cooling device (until Day 28 or ICU discharge)
- Proportion of patients requiring discontinuation of physical cooling because of shivering (censored at Day 28)
- Proportion of patients receiving paralysing drugs in the ICU (excluding for intubation) (until Day 28 or ICU discharge)
- Proportion of patients receiving propofol and average daily dose received in the first 7 days in the ICU after randomisation
- Proportion of patients receiving morphine (or morphine equivalents of other opioids) and average daily dose received in the first 7 days in the ICU after randomisation
- Proportion of patients receiving midazolam (or midazolam equivalents of other benzodiazepines) and average daily dose received in the first 7 days in the ICU after randomisation
- Proportion of patients receiving dexmedetomidine and highest hourly rate of infusion ($\mu\text{g}/\text{kg}/\text{h}$) on each of the first 7 days in the ICU after randomisation
- Proportion of patients receiving norepinephrine and highest hourly rate of norepinephrine administration ($\mu\text{g}/\text{kg}/\text{min}$) on each of the first 7 days in the ICU after randomisation
- Proportion of patients receiving epinephrine and highest hourly rate of epinephrine administration ($\mu\text{g}/\text{kg}/\text{min}$) on each of the first 7 days in the ICU after randomisation
- Proportion of patients receiving each of the following drugs by infusion on each of the first 7 days in the ICU after randomisation (dobutamine, milrinone, dopamine, metaraminol, phenylephrine, vasopressin, levosimendan)

ICU = intensive care unit. IV = intravenous.

Table 3. Planned tables and figures

- Table 1: characteristics of patients at baseline, by treatment group
- Table 2: study outcomes, by treatment group (primary and secondary outcome variables)
- Table 3: process-of-care measures related to temperature control, by treatment group (mean dose of paracetamol, proportion of paracetamol administered by the IV route, proportion of patients treated with a physical cooling device, duration of cooling with a physical cooling device, proportion of patients requiring discontinuation of physical cooling because of shivering)
- Table 4: key process-of-care measures, by treatment group (ICU length of stay, hospital length of stay, ventilator-free days, vasopressor-free days, new post-randomisation RRT use, days of IV antibiotics, number of sets of blood cultures performed)
- Table S1: additional temperature variables, by treatment group (proportion of patients with body temperature in the ICU of $\geq 38.3^{\circ}\text{C}$ and with body temperature in ICU of $\geq 39^{\circ}\text{C}$)
- Table S2: AST, ALT, ALP, GGT, bilirubin and creatinine levels, by treatment group
- Table S3: proportion of patients requiring sedative, paralysing and vasoactive drugs, by treatment group
- Table S4: doses of sedatives and vasoactive drugs, by treatment group
- Table S5: adverse events, by treatment group
- Figure 1: participant flow diagram
- Figure 2: Kaplan–Meier estimates of the probability of survival to Day 90
- Figure 3: 6-hourly temperature, heart rate, respiratory rate and mean arterial pressure, by treatment group
- Figure S1: highest daily temperature in the ICU, by treatment group

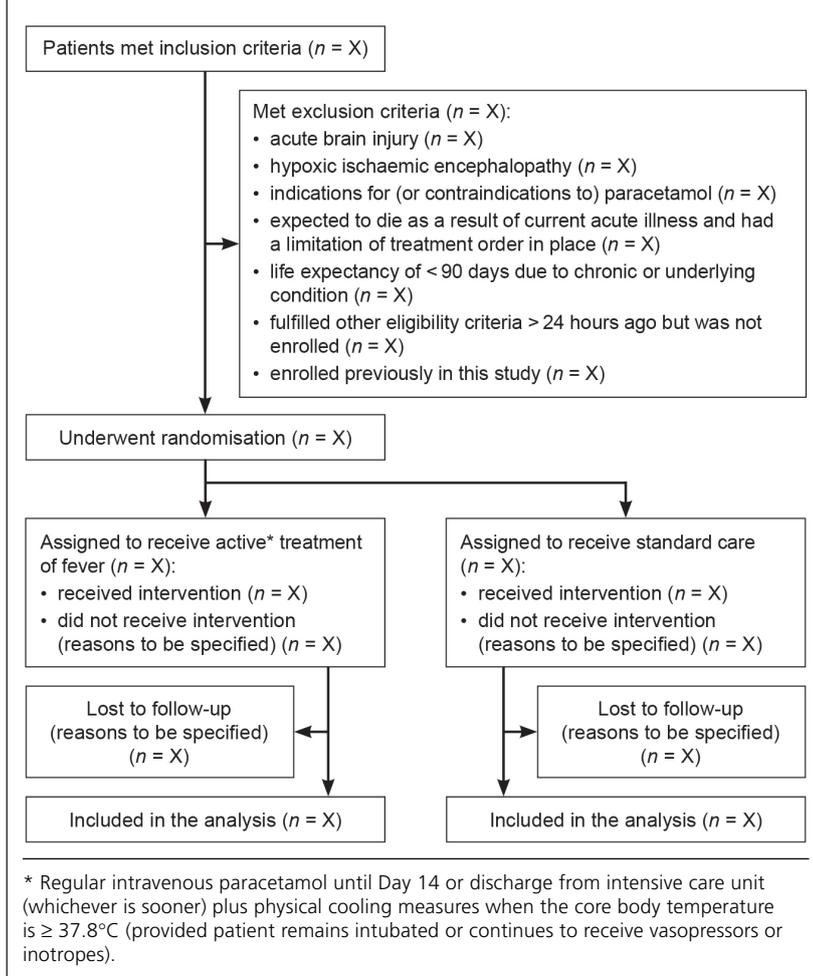
IV = intravenous. ICU = intensive care unit. RRT = renal replacement therapy. AST = aspartate aminotransferase. ALT = alanine aminotransferase. ALP = alkaline phosphatase. GGT = gamma-glutamyltransferase.

generated random numbers. Participants will be enrolled in the study by ICU doctors, nurses and research staff, and the assigned intervention will be communicated to the bedside nurse who will implement the study interventions.

Data collection

Trained research coordinators will collect data at each site. Study data will be entered on a paper case report form,

which will be scanned and emailed to the coordinating centre and reviewed for internal consistency by trained project managers. Any data queries arising will be addressed by the research coordinators at the study centres. When data have been reviewed and approved, they will be entered into a study database using double data entry to create duplicate datasets, which will then be compared. Any disparities between datasets will be resolved by reviewing paper case

Figure 2. Plan for presenting participant flow data

report forms and consulting site research coordinators if necessary. We do not plan any onsite source data verification for this study.

Baseline data will be:

- patient demographic information (age, sex and ethnicity)
- ICU admission diagnosis
- ICU admission category (elective or emergency surgical or medical)
- Acute Physiology and Chronic Health Evaluation (APACHE) II score
- whether or not the patient has a known or suspected infection that is being treated with antimicrobials.

Daily data will be collected from Day 0 (the day of randomisation) until Day 28 (672 hours after randomisation). The primary outcome will be assessed at Day 7, and secondary outcomes will be assessed at Day 28 or Day 90, as appropriate.

Power and sample size

Our sample size of 184 patients will provide 90% power to detect an effect size of 0.3°C , based on a standard deviation (SD) of 0.68, using a two-tailed hypothesis and an alpha of 0.05, and allowing for a 5% drop-out rate.

Statistical analysis

We will analyse data on an intention-to-treat basis without imputation of missing data, and all data will initially be assessed for normality. Treatment group comparisons will be performed using χ^2 tests for equal proportion, the Student t test for normally distributed data, and Wilcoxon rank-sum tests otherwise, with results reported as n with percentages, means with SDs, and medians with interquartile ranges (IQRs), respectively.

To account for repeat measures, we will analyse the primary outcome (body temperature) using mixed linear modelling, with each patient treated as a random effect and results reported as least-square means with 95% CIs.

We will analyse in-hospital mortality and survival time using logistic regression and Cox proportional hazards regression, respectively, and will report results as absolute and relative risk differences, odds ratios with 95% CIs, and hazard ratios with 95% CIs. Survival analysis will be presented using the Kaplan–Meier survival curves with group comparison using a log-rank test.

We will conduct sensitivity analysis for temperature and mortality, adjusting for any baseline imbalances, sites and pre-defined covariates (baseline temperature, age and APACHE II score) using hierarchical mixed modelling, with patients nested within sites and sites treated as a random effect.

ICU-free days will be compared using Wilcoxon rank-sum tests but, to facilitate future sample size calculations, we will report them as means with SDs and medians with IQRs. Duration variables (ICU and hospital lengths of stay) will be log-transformed when appropriate, and for increased interpretability will be further stratified and reported by survival status.

We will perform pre-specified subgroup analysis using the “known or suspected infection versus all others” pre-randomisation subgroups.

Heterogeneity between outcomes and subgroups will be determined by fitting an interaction between treatment and subgroup. For future planning, eligible enrolled patients will be compared against eligible non-enrolled patients. Specifically, we will collect the Australian and New Zealand

Intensive Care Society Centre for Outcome and Resource Evaluation (ANZICS-CORE) Adult Patient Database (APD) number for all eligible patients and will then compare enrolled and non-enrolled patients for all variables available in the ANZICS-CORE APD. We will perform all analyses using SAS, version 9.4 (SAS Institute), and statistical significance will be defined as two-sided $P < 0.05$. We will make no adjustment for multiple comparisons.

Safety

Approvals

This study is approved by the New Zealand Northern A Health and Disability Ethics Committee (16NTA111) and the Northern Sydney Local Health District Human Research Ethics Committee (HREC/16/HAWKE/328). The study was prospectively registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12616001285448).

Data monitoring committee

The members of the data monitoring committee (DMC) will be Professor Jeff Lipman (Chair) and Professor Michael Reade. The role of the DMC is to ensure that the rights and safety of patients involved in the study are protected by reviewing reported adverse events and making recommendations to the REACTOR management committee. The DMC has reviewed the trial protocol, agrees with the statistical approach taken and will review and advise the REACTOR management committee on any proposed protocol modifications. We plan no interim analysis for this trial, but the DMC has the right to review study data (blinded or unblinded) related to the safe conduct of the study at any time. The DMC acts in an advisory capacity to the REACTOR management committee members, who are ultimately responsible for the running of the trial. The REACTOR management committee will update the DMC on accumulating external evidence relevant to the study in a timely manner, and the DMC will advise the REACTOR management committee on the importance of this evidence to the further conduct of the study.

Adverse events

Intensive care patients frequently have abnormal laboratory test results, signs and symptoms, and life-threatening organ failure unrelated to study interventions and despite optimal management. Therefore, in accordance with established practice in academic ICU trials,¹⁸ events that are part of the natural history of the primary disease process, expected complications of critical illness or study outcomes will not be routinely reported as adverse events in this study. All adverse events that are considered to be potentially causally related to the study intervention or are otherwise of concern, at the judgement of the investigator, will be reported.

The following ICU adverse event data, censored at Day 28, will be systematically measured, collected and stated in the final report:

- proportion of patients with shivering
- number of shivering episodes per patient per day
- proportion of patients with new post-randomisation bacteraemia (excluding skin contaminants).

These events will not be individually reported using adverse event reporting systems at the time they occur unless, in the investigator's judgement, they are considered to be of concern.

Summary

The REACTOR trial is a multicentre, phase II, parallel-group, randomised controlled superiority trial. The trial will compare active control of fever with standard management of fever in mechanically ventilated adults in the ICU without acute brain injury, who are expected to be ventilated beyond the day after randomisation. If a systematic approach to active temperature control reduces mean body temperature, it is plausible that this approach might improve clinical outcomes for critically ill patients with limited functional reserve who are less able to respond to the physiological demands created by fever. This study is part of a larger research program that is being conducted to help inform the design of future clinical trials investigating strategies of temperature control in critically ill patients.

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Competing interests

None declared.

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