Sex representation within ICU clinical trials in Australia and New Zealand

Protocol and Statistical Analysis Plan

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Background:

Clinical trials should include a study population that represents the intended target population – the group of patients affected by the illness in question –to maximise the generalizability of their findings. If a demographic group is under-represented in a clinical trial population, the findings of that trial may be relatively less applicable to this group. This leads to knowledge gaps about the benefits or harms of the tested interventions when applied to the under-represented group.

Sex balance is one dimension of representation in clinical trials. That is, whether the proportion of female, male or non-binary patients in the study population approximates the proportions within the target population. Major international research governance bodies now recognize sex and gender as key demographic factors that require specific attention in clinical trials. For example, the National Institute of Health (NIH, USA) require all NIH-supported trials to consider sex in trial design, and collect, analyse and report sex-based data.[1]

Steinberg and colleagues examined over 20,000 clinical trials across a variety of disciplines, observing that the sex representation varied according to disease category and the type of intervention; both female and male participants were underrepresented in different areas.[2] This study did not examine ICU-specific clinical trials. Kristensen and colleagues examined ICU randomized controlled-trials published in 2011-2023, reporting that most had a significant sex imbalance in their study population and many did not attend to sex disparities between randomized groups.[3] However, there are consistently fewer women than men among patients admitted to the ICU and sex balance varies across diagnostic groups of ICU patients.[3] Therefore it remains unclear if ICU RCTs include female, male and non-binary patients in proportions representative of their respective target population.

Accordingly, we undertook a study comparing the sex balance – defined as percentage of population who were female, male and non-binary sex – in the study populations of RCTs undertaken in Australia and New Zealand ICUs and their corresponding target populations. We examined clinical trials endorsed by the Australia and New Zealand Intensive Care Society (ANZICS) Clinical trials group and completed between 2014 and June 2023. We identified corresponding target population using the ANZICS Adult Patient Database, a major clinical registry that records approximately 90% of all admissions to ICUs in Australia and New Zealand. We hypothesized that the percentage of female patients within each study population was lower than the percentage of female patients in matched target population, and that non-binary patients were not represented in these study populations.

Study question:

Do contemporary randomised controlled trials (RCTs) conducted in Australia and New Zealand intensive care units (ICUs) include male, female and non-binary patients in proportions representative of their target populations?

Primary Objectives

To compare the sex balance; defined as percentage of population who were female, male and non-binary sex; of the study populations of CTG-endorsed RCTs and corresponding target populations matched from the APD.

Secondary objectives:

- To identify any changes in the sex-based representativeness of CTG trials over time and between diagnostic groups
- To identify how many completed trials reported on sex-based subgroup analysis

Hypotheses:

- That the percentage of female patients within each study population is lower than the percentage of female patients in the target population of ICU patients with matched characteristics.
- That non-binary patients (patients classified as a third sex, neither female or male) are not represented in the study populations of ICU

Methods

Population:

Inclusion criteria:

Adult patients (as defined by trial) randomized in ANZICS CTG-endorsed randomized clinical trials

- Trials listed 'completed' 2014-30 June 2023 by ANZICS CTG (https://www.anzics.com.au/completed-research)
- Trials that included >/= 100 participants from 5 or more hospital sites in Australia and New Zealand

Exclusion criteria

- Paediatric ICU trials
- Trials that included <100 participants
- Trials that recruited participants from fewer than 5 hospital sites in Australia and New Zealand

Matched target populations:

ICU patients with admissions recorded in the ANZICS APD and matched according to all possible trial inclusion and exclusion criteria. We will publish a list of all inclusion and exclusion criteria for each trial in supplement; and note for each inclusion and exclusion criteria:

  - Whether it could be matched using APD data
  - How it was matched

We will assess the quality of matching for a pre-specified sensitivity analysis including only well-matched trials (see below). Populations will be judged well matched if they could be *matched to the inclusion criteria* across 4 or more of these 5 criteria:

i. recruitment period (time)
ii. age of participants
iii. diagnostic group (e.g. TBI)
iv. treatment in ICU (e.g. mechanical ventilation)
v. recruiting units

Definition of exposure: sex balance

Sex balance defined as % patients in a population who are female, male and non-binary
Sex as recorded in hospital records and transcribed into APD:

- Male
- Female
- Non-binary sex, labelled 'intersex/indeterminate' in APD

Statistical Analysis

- Categorical variables were reported as counts with percentages to one decimal place.
- To compare the percentage of female patients within each trial and the matched APD population, two overlapping or non-independent populations, we used the following calculation:

  $(p - \theta)/V$, where V is $\sqrt{(\theta(1-\theta)) / n}$, compared to standard normal

  Where:
  θ = proportion of women in matched APD population
  p = proportion of women in RCT study population
  n= study population (sample size)
- The percentage non-binary will be analysed in the same way
- Subgroup analysis (subgroups defined below):
- P<0.05 taken to indicate statistical significance, 95% confidence intervals reported
- Statistical analyses performed with STATA 17 BE (Statacorp, Texas USA)

Subgroup analysis:

1. Change over time:
   a. 'Early' (trials completed 2014 -2018) vs 'late' (trials completed 2019-2023)
2. Diagnostic cohort
   - All-comers (broad range of diagnostic categories included)
   - Sepsis
   - Trauma
3. Consent-type
   a. Waived
   b. Consent to enrol/consent to continue

Sensitivity analysis

1. Excluding all studies judged poorly matched, as defined above

Planned figures and tables

Figure 1: Trial inclusion flow diagram

Table 1: Characteristics of included trials*

Study title, author, publication year	Trial intervention	Study population (n)	Recruitment period	Key inclusion criteria	Multinational trial?

*complete list of inclusion and exclusion criteria included in supplementary table X

Table 2: characteristics of trial participants & matched APD populations

Trial population					Matched APD population					
Study title/year	*n*	Female patients, n (%)	Age, mean (SD)	APACHE II score	Elective surgery N (%)	*n*	% female	Age, mean (SD)	APACHE II score	Elective surgery, n (%)
Trial 1										
Trial 2										

Figure 2: Forest plot of sex balance of trial population compared to APD-matched target populations, by subgroup.

References

1. National Institutes of Health. NIH Policy on Sex as a Biological Variable. 2016. https://orwh.od.nih.gov/sex-gender/nih-policy-sex-biological-variable (accessed 28th August 2023.
2. Steinberg JR, Turner BE, Weeks BT, et al. Analysis of Female Enrollment and Participant Sex by Burden of Disease in US Clinical Trials Between 2000 and 2020. *JAMA Netw Open* 2021; **4**(6): e2113749.
3. Kristensen ML, Vestergaard TR, Bulow HH. Gender differences in randomised, controlled trials in intensive care units. *Acta Anaesthesiol Scand* 2014; **58**(7): 788-93.
4. Modra LJ, Pilcher D, Bailey M, Bellomo R: Sex differences in Intensive Care Unit Admissions in Australia and New Zealand. ***Crit Care and Resusc*** 2021; 23:86-93