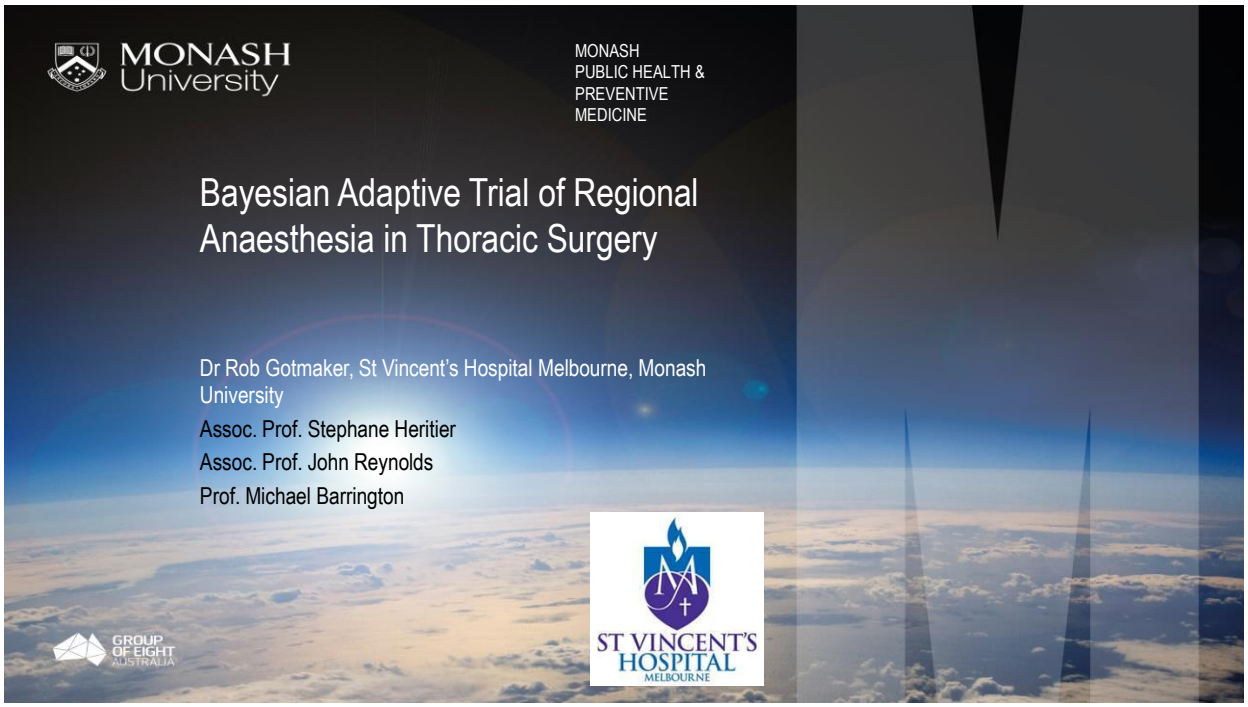
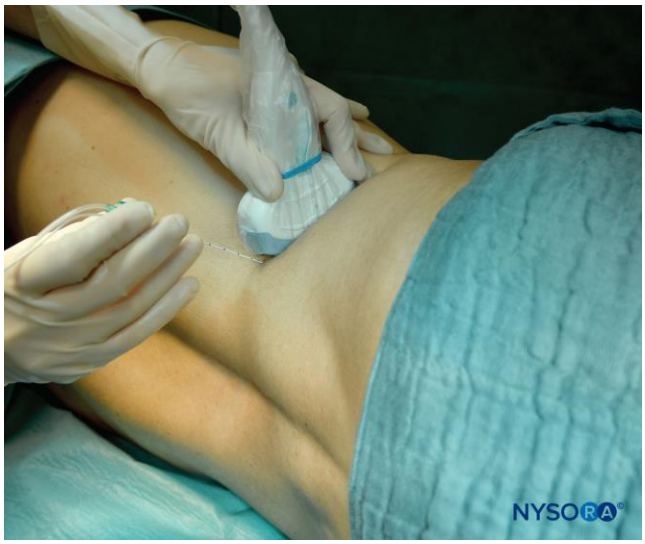


The presenter has advised that the following presentation is subject to no conflicts of interest and has nothing to disclose.

Background

- Regional anaesthesia
  - use of local anaesthetic to reduce sensation in specific body parts
- Concern over opiate use due to “US opiate epidemic”
- Waning enthusiasm for established techniques such as epidurals over safety concerns
- New regional anaesthesia techniques are being continuously described
  - In particular, many new interfascial plane blocks have been described
  - Thought to be safe and easy to perform
- Evidence failing to keep pace with practice
  - Unknowns: efficacy, indications, dosing regimens
- We propose a multi-arm blinded adaptive trial to simultaneously assess multiple regional anaesthesia interventions

Quadratus lumborum block (image from https://www.nysora.com)



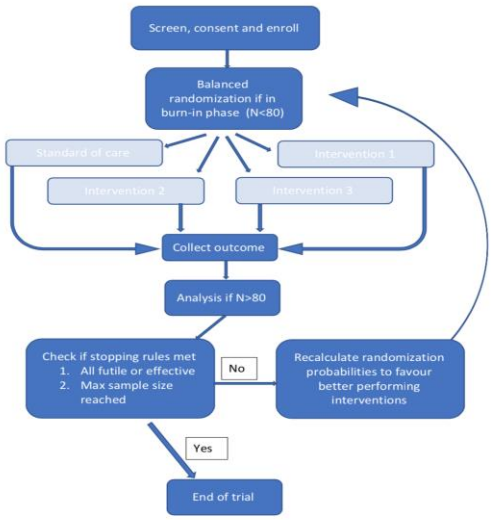
Trial design

- Bayesian adaptive design with RAR and early stopping for futility and efficacy
  - *Adapted from endTB trial, Cellamare, Trippa et al.*
    - Multiarm trial in Tuberculosis, uses response adaptive randomization (RAR) and early stopping for futility, binary outcome
- Elective thoracic surgery patients
- 4 arms
  - Usual care (including any routine local anaesthesia) + inactive catheter infusion
  - Erector spinae block + catheter infusion
  - Mid-point transverse process to pleura block + catheter infusion
  - Paravertebral block + catheter infusion
- Primary outcome is the Quality of Recovery Score (QoR15) at 24 hours
  - 15 questions PROM, (regarding pain, nausea, ability to breath, emotional support, etc.)
  - Can be transformed to be approximately normally distributed

MONASH University

5

Trial Design

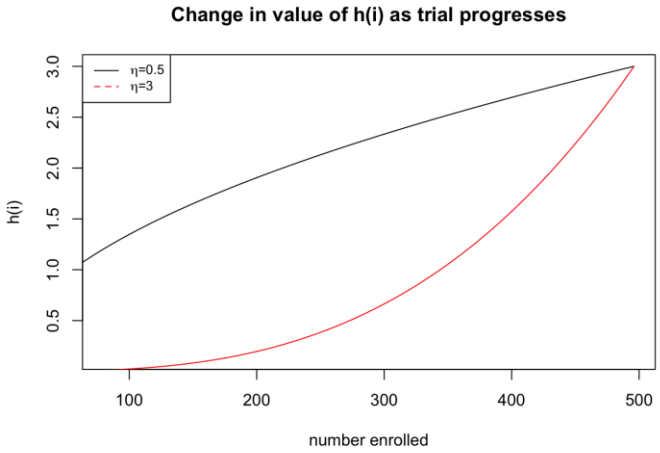


- After a burn-in period, **randomization is gradually unbalanced** towards better performing arms.
- The **control arm size is matched** to the best performing arm to maintain statistical efficiency
- The **entire trial stops if all arms** are found **futile** or **efficacious** or if the maximum sample size is reached
- **Adaptive rules are predefined** and do not change after trial starts
- **Adaptations are tuned** to achieve the desired frequentist operating characteristics through computer simulation

MONASH University

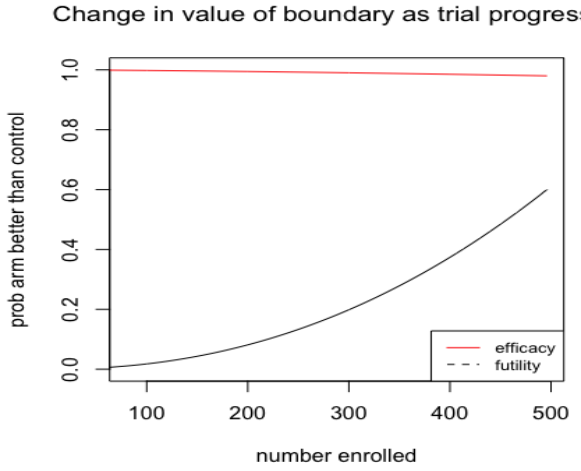
6

Response adaptive randomization



- $p_i(k) \propto \frac{P(QoR_{median}\ arm\ k > QoR_{median}\ control \mid data)^{h(i)}}{\sum_{j=1}^{3} P(QoR_{median}\ arm\ j > QoR_{median}\ control \mid data)^{h(i)}}$
- Probability of group assignment is proportional to the probability that that group is superior to control
- The rule is tuned with a function, *h(i),* to allow RAR to ramp up as more data accumulate
- Reduces the risk of adapting to noisy data early in the trial

Futility and efficacy boundaries



Possible advantages of adaptive design

- Shared controls (common to all multi-arm studies)
- Able to direct resources to most promising treatments
  - Gather more information about effective treatments
  - Essentially moving from from pilot stage to confirmatory stage in one trial
- Smaller sample size
- Increased ability to detect efficacy (power) for a given total sample size (if at least one treatment is poor)
- Maybe more ethical if more patients in a trial receive effective treatments

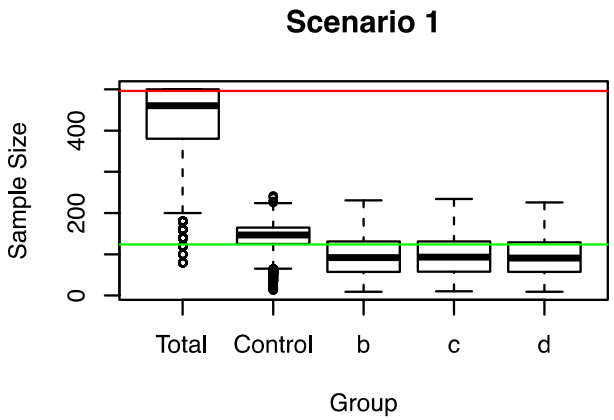
Equivalent frequentist design- Sample size

- Conventional 2 arm study
  - To detect a difference of 8 (MCID) on the QoR15 scale (assuming median QoR15 107)
  - NEED 248 patients
- To study 3 interventions with 3 controls in series
  - NEED 744 patients
- Fixed randomisation multi-arm trial
  - NEED 496 patients, therefore save 250 patients by going multi-arm alone

Simulation to determine the operating characteristics

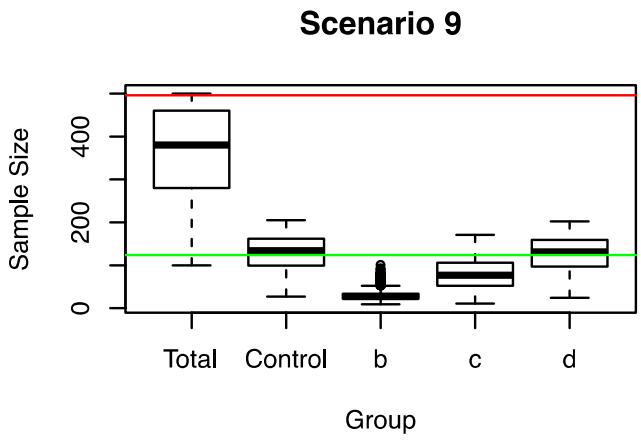
- Bayesian design-no closed form power analysis
  - Need to simulate the design
- 9 combinations of efficacious and inefficacious arms
  - For example
    - All arms inactive (same mean as control)
    - All arms active (means greater than control)
    - 1 effective, 1 detrimental arm
- By tuning the adaptations we have found a design that
  - Maintains 80% power if all arms are effective
  - Keeps one-sided pairwise type I error to 2.5% if all arms ineffective
  - Reduces median sample size in all scenarios
    - Mean simulated sample size was 395 – 466

Simulation



- All interventions are ineffective
- On average, more patients are allocated to control
- Control matches the group that (randomly) is largest
- Type 1 error for each arm is 2.1%
- Expected sample size is moderately reduced

Simulation



- Group d- Superior
- Group b- Inferior
- Group c- No effect

- Control sample size matches best performing arm by design
- Power for group d approaches 100%
- Type 1 error for group b approaches 0

Criticisms and limitations of adaptive design

- Simulation and planning phase is time consuming
  - Especially as the trial/model complexity increases
  - This simulation was coded in R and run on a cluster
- Acceptance/Communication of results to
  - collaborators, funders, ethics, journals, etc
  - improving
- Greater risk of estimation bias compared to fixed design
  - e.g. drift, early stopping
- Risk of group imbalance in the wrong direction
- Sample size variance
- Require short term outcome or surrogate outcome to drive randomisation
- Not suitable for all clinical questions

For more detail

Trippa L, Lee EQ, Wen PY, Batchelor TT, Cloughesy T, Parmigiani G, et al. Bayesian adaptive randomized trial design for patients with recurrent glioblastoma. *J Clin Oncol* 2012;30:3258-63.

Cellamare M, Ventz S, Baudin E, Mitnick CD, Trippa L. A Bayesian response-adaptive trial in tuberculosis: The endTB trial. *Clin Trials* 2017;14:17-28.

Gotmaker R, Barrington MJ, Reynolds J, Trippa L, Heritier S. Bayesian adaptive design: the future for regional anesthesia trials? *Reg Anesth Pain Med.* Mar 2 2019.