# Whole-of-life inclusion in Bayesian adaptive platform clinical trials

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# Abstract Importance

There is a recognized unmet need for clinical trials to provide evidence-informed care for infants, children and adolescents. Here we outline the capacity of three distinct trial design strategies; sequential, parallel, and unified adult-pediatric Bayesian adaptive design, to incorporate children into clinical trials and transform this current state of evidence inequity. Additionally, we demonstrate a unified adult-pediatric whole-of-life clinical trial through the *Staphylococcus aureus* Network Adaptive Platform (SNAP) trial (NCT05137119).

# Observations

Bayesian methods provide a framework for synthesising data in the form of a probability model that can be used in the design and analysis of a clinical trial. Three trial design strategies are compared: (i) a sequential adult-pediatric Bayesian approach that involves a separate, deferred pediatric trial that incorporates existing adult trial data into the analysis model to potentially reduce the pediatric-trial sample size, (ii) a parallel adult-pediatric Bayesian trial whereby separate pediatric enrolment occurs in a parallel trial, running alongside an adult RCT; and (iii) a unified adult-pediatric Bayesian adaptive design that supports the enrolment of both children and adults simultaneously in a whole-of-life Bayesian adaptive RCT.

The SNAP trial ‘whole-of-life’ design uses a Bayesian hierarchical model that allows information sharing (also known as “borrowing”) between trial age groups by linking intervention effects of children and adults, thereby improving inference in both groups.

# Conclusion and relevance

Bayesian hierarchical models may provide more precision for estimates of safety and efficacy of treatments in trials with heterogenous populations compared to traditional methods of analysis. They facilitate the inclusion of children in clinical trials and a shift from children

deemed “therapeutic orphans” to the vision by Halpern and colleagues of “no child left

behind” in clinical trials to ensure evidence for clinical practice exists across the life course. The SNAP trial provides an example of a Bayesian adaptive whole-of-life inclusion design that enhances trial population inclusivity and diversity overall, as well as generalisability, and translation of findings into clinical practice

**Sub-title:** Special communication

Introduction

There is a recognized unmet need for clinical trials to provide evidence-informed care for infants, children and adolescents1. While clinical trials that serve the needs of children alone are one option, incorporation of children into whole-of-life inclusive clinical trials is both pragmatic and an efficient means to address this unmet need2. Throughout the COVID-19 pandemic, increased advocacy for diversity in clinical trial participants has occurred for many underrepresented groups, including children3 and pregnant women4. Despite this, many of these cohorts were deprived of high-quality evidence to inform best-practice treatment decisions for COVID-19. This evidence inequity was well established pre-COVID, with an estimated 90% of therapies provided for children overall yet to be tested through clinical trials and 62% of pediatric trials delayed or incomplete5. Some of the reasons for this inequity may be perceived barriers by investigators and industry6. Exclusion of children from clinical trials has become increasingly normalized without justification, particularly in the setting of low-risk trials where the study condition occurs across the life course1,7. Novel approaches to trial design and a fundamental shift to inclusion of children is critical to improve the timeliness and quality of evidence informing treatment strategies.

The United States Food and Drug Administration recently published guidance on Bayesian trial design use to enhance diversity of clinical trial populations8. This framework for trial design offers advantages over traditional approaches, particularly to facilitate inclusion of

children.8 Here we outline the capacity of three distinct trial design strategies: sequential; parallel; and unified adult-pediatric Bayesian design; to incorporate children into clinical trials and transform the current state of evidence inequity. We demonstrate a unified adult- pediatric whole-of-life clinical trial through the *Staphylococcus aureus* Network Adaptive Platform (SNAP) trial (<https://www.snaptrial.com.au/>) (NCT05137119)9 encompassing the

pediatric cohort; SNAP-pediatric and Youth (SNAP-PY).

*i. Approaches to Bayesian trial design for generation of pediatric-specific evidence*

A Bayesian approach provides a framework for synthesising data in the form of a probability model that can be used in design and analysis of a clinical trial10. In addition, adaptive designs use scheduled analyses of the accumulating trial data to inform pre-defined trial operating decisions10. Because of their flexibility, Bayesian methods are increasingly used to design and analyse adaptive clinical trials. Traditional randomized controlled trials (RCTs) are commonly designed with a fixed sample size and often under-powered in the pediatric setting, resulting in relatively high uncertainty around clinical effects compared to adult populations11. An adaptive trial can employ strategies to mitigate risks associated with fixed sample sizes12. For example, an adaptive design may minimise the number of participants exposed to inferior treatments (i.e avoid overpowering a trial) by stopping the trial at an interim analysis if a stronger than expected treatment effect is observed or it may avoid underpowering a trial often due to a weaker than expected treatment effect, by continuing enrolment until pre-specified stopping rules are reached13. Advanced Bayesian adaptive platform designs can investigate multiple research questions involving multiple treatments in heterogenous populations simultaneously,

facilitating inclusion of children in clinical trials8. This importantly enables children to be beneficiaries of clinical trial evidence.

*A sequential adult-pediatric Bayesian trial*

A sequential Bayesian approach involves a separate subsequent pediatric trial that incorporates existing adult trial data into the statistical model to facilitate a potential reduction in sample size. International guidance on this sequential Bayesian model in smaller trial populations has resulted in increasing numbers of pediatric trials adopting this methodology14. In this strategy the treatment effect among children is linked to an estimate of the treatment effect among adults through a hierarichal model15. This design increases statistical power and precision whenever the treatment effect in the pediatric group is concordant with a predefined estimate from the adult data and is largely unaffected if the treatment effects are discordant2,14,15. This strategy may be suitable for exploratory phase II research, such as those conducted in emerging biologics for pediatric systemic lupus erythematosus16. Importantly in drug discovery this allows initial safety data to be established in adults, yet still improves feasibility for subsequent pediatric trial design and reduced trial costs. However, this deferred sequential model does not address the time delays to establishing clinical trial evidence in children. This design for comparative effectiveness trials may also result in decreased clinician equipoise, or funding availability due to the belief that clinical trial evidence for adults is sufficient and can be extrapolated to children without direct evidence 17. This is reflected in the fact that almost half (45%) of all medications for children are prescribed off label7.

*A parallel adult-pediatric Bayesian trial*

An alternative strategy for generating evidence for children is separate pediatric enrolment in a parallel trial, running alongside an adult RCT. Bayesian methods under this strategy are predominantly applied to the use of historical controls to inform predefined treatment estimates for the statistical model. This may be appropriate when study interventions or endpoints cannot be harmonized across pediatric and adult populations, such as in a recent acute lymphoblastic leukemia trial for selumetibinib18. Advantages of a parallel strategy over a sequential approach include more rapid generation of evidence for children and facilitation of shared trial infrastructure, statistical support, and collaborative learning. Running two separate, parallel trials may however incur considerable costs and planning and is appropriate only when safety data is available to proceed the parallel trial. Additionally, a lack of data integration can result in uncertainty as to whether an intervention’s efficacy across age- groups is due to protocol or true difference, such as that encountered in adult19 and pediatric20 ventilator weaning trials.

*A unified adult-pediatric Bayesian trial – whole-of-life inclusion strategy*

There have been recent calls in the literature supporting the enrolment of both children and adults in unified Bayesian adaptive RCTs, 2,17 however this requires significant collaboration and development of effective partnerships between pediatric and adult clinical trialists in the planning and execution phases of a study. Changing mindsets to include children and adults in a single harmonized clinical trial involves challenging the status quo. This whole-of-life approach requires investigators to align study endpoints, data collection and management infrastructure into a single master protocol inclusive of participants of all ages12. Through a Bayesian hierarchical model, information from adult and pediatric data is able to be shared by linking treatment effect parameters in both groups17. Because patients are enrolled concurrently in the same trial, this unified approach reduces concern regarding the

appropriateness of using historical trial data. For diseases that do not occur across the life course or where study endpoints would be inappropriate to harmonise, other trial designs such as a parallel adult-pediatric Bayesian trial or a stand-alone pediatric trial may be more appropriate. Where research questions may not have clinician equipoise to unify across the life course (e.g different disease phenotypes), the Bayesian adaptive platform design has the flexibility to exclude a domain (sets of treatments that share a common modality) within a trial for subgroups such as children and conversely, to add domains for all or specific subgroups. Such designs increase trial complexity with additional statistical expertise and planning required, however consolidation of trial infrastructure, and a centralised ethical review board may enhance cost-effectiveness21. To the best of our knowledge, the SNAP trial is one of a limited number of whole-of-life trial participant inclusion models in a Bayesian adaptive RCT.9

*ii) Whole-of-life inclusion – The Staphylococcus aureus Network Adaptive Platform (SNAP) trial*

Addressing a multitude of treatment questions including optimal antimicrobial agent, route and duration of treatment are required for a range of infectious diseases occurring across the age continuum. One such example is *Staphylococcus aureus,* the leading bacterial cause of global mortality overall, with an estimated >1 million *S. aureus* infection related deaths per year22. Despite an incidence of 4-26/100,000 children/year23-25 and 20-50/100,000 adults/year26,27, fewer than 300 children28 worldwide have ever been enrolled in *S. aureus* bacteraemia (SAB) clinical trials, and optimal antibiotic treatments have not been established. It is unknown whether pediatricians optimally treat SAB in children, as they rely on predominantly adult data to guide treatments decisions which may lead to potential harm

(such as over treatment with intravenous antibiotic therapy, vancomycin associated nephrotoxicity, prolonged hospital admission), or less effective treatments based on extrapolated adult data28.

*Study design and setting*

The SNAP trial is an international multicentre, pragmatic, multi-arm, open-label adaptive platform trial addressing multiple therapeutic questions concurrently in individuals with SAB9. SNAP is a comparative effectiveness trial that is currently enrolling neonates through to elderly adults and has harmonized aims across the life-course including: finding the best antibiotic for SAB treatment based on antibiotic susceptibility profile; estimating the effect of the addition of adjunctive clindamycin to standard care; and determining the effectiveness and safety of a switch from intravenous to oral antibiotic therapy at 7 or 14 days (+/- 2 days) to complete SAB treatment9. Each question is addressed in parallel by randomising participants within active domains (sets of treatments that share a common modality), i.e at trial commencement this consisted of a backbone antibiotic domain, an adjunctive antibiotic domain, and an early oral switch domain.

All trial endpoints, including the primary endpoint (90-day all-cause mortality) and secondary endpoints apply across age-groups (Table 1)29. Based on previous studies, there are increased similarities between neonatal and middle-aged adult SAB all-cause mortality (23% vs 19- 28%)30, compared with older adults (85 years; 58%)27, and children overall (2.6%), highlighting the limitations of arbitrary age-based clinical trial models2. These data also underscore a key issue in designing a trial with a harmonized primary endpoint of all-cause mortality; powering on all-cause mortality in children alone would require a prohibitively large sample size, however incorporating the heterogeneity of event rates within trial sub-

populations (adult and children) also poses considerable statistical challenges. To provide additional power for secondary analyses, we have constructed a pediatric specific composite endpoint that includes four of the secondary endpoints (Table 1)29. Based on data from a prospective pediatric cohort of SAB, we estimate that 30% of the pediatric trial population will meet this composite endpoint29.

*Study participants*

This large scale RCT is pragmatic, with exclusion criteria kept to a minimum, regardless of an individual’s age or pregnancy status31 (eTable 1 in the Supplement). Data is collected from routine clinical care and all trial interventions are open label and currently available treatments for SAB. Participant recruitment in Australia is performed through simplified layered consent and assent, established with community feedback, inclusive of adolescents with lived experience of SAB32. This layered consent model to date has not yet been accepted by research ethics committees in New Zealand or Canada.

*Study sample size*

The SNAP trial will aim to enrol up to 7,000 patients (6,000 adults, 1,000 children) across multiple countries over five-years. Trial operating characteristics such as Type I error (false positive rates) and probability of reaching decision thresholds, were estimated from computer simulations that account for many different hypothetical trial scenarios and are summarised in Mahar et al33.

*Randomisation procedures*

Participants are randomly allocated into a single arm within each of the multiple domains using a web-based module (eFigure 1 and eTable 2 in the Supplement). Intervention

assignments are blinded up to the commencement of the trial antibiotic treatment, whereby the randomization is revealed, and open label thereafter.

*Statistical procedures*

As an adaptive platform trial, SNAP required greater pre-trial planning compared with a traditional design. Following extensive discussions with the SNAP Trial Steering Committee to facilitate inclusion of children, the statistical team simulated trial data under many different treatment effect scenarios for the pediatric and adult populations to inform stopping rules for the trial. Since commencement of the trial in February 2022, interim Bayesian statistical analyses are performed after every 500 participants complete 90-day follow-up, until a pre- defined decision rule for superiority, non-inferiority or futility is met (e.g. when an intervention has > 99% probability of being superior or non-inferior). This ongoing scheduled data analysis during the trial, in general decreases the time to reach a trial conclusion, and may result in fewer participants assigned to inferior treatments, allowing the least number of children to be exposed to inferior treatments 34. Future interventions and/or domains may be added over time as trial conclusions are reached. This design also facilitates pediatric sub-

studies planned for SNAP including drug pharmacokinetic-pharmacodynamic, imaging modalities and microbiological analyses.

The SNAP trial ‘whole-of-life’ design is based around a Bayesian hierarchical model that allows information sharing between trial age groups by linking intervention effects of children and adults, thereby improving inference in both groups33. The primary statistical model provides treatment effect estimates for both pediatric (child [0-17 years] and adult [18+ years]) subgroups after adjustment for covariates, including more detailed age- groupings of (‘30 days or less’, ‘31–365 days’, ‘1–4 years’, ‘5–12 years’, ‘12–17 years’,

‘18–39 years’, ‘40–59 years’, ‘60–79 years’, ‘80 years and over’)33. Decision thresholds for discontinuing randomization will be restricted to the intervention effects in the adult population and not in the pediatric population. Limitations of this model include the possibility of heterogenous effects between adult and paediatric participants, however the platform allows for flexibility to re-open domains if heterogenous treatment effects are apparent and there is sufficient equipoise to recruit again within sub-populations. Hierarchical borrowing will occur from the pediatric population to inform the adult efficacy estimates, given the relatively small sample size and lower mortality rates in the pediatric trial population. When decision rules are met and trial conclusions reported, there will also be separate reporting of the intervention effects stratified by age. This will allow an assessment of how similar the intervention effects are in both direction and size and will provide greater confidence that the overall intervention effect likely applies to varying age groups within the trial. This design approach is significantly more refined than extrapolating adult data to children and allows a more bespoke approach to assessing safety and efficacy of treatments within trial populations.

*Trial infrastructure and funding*

Pediatric investigators are part of the SNAP global trial steering committee and have contributed to the master trial protocol, domain-specific appendices and pediatric appendix. There is a pediatric investigator on each working group and sub-committee across the trial, as well as on the independent, international data safety monitoring committee (DSMC). The SNAP trial has successfully attracted funding from multiple national health research funding bodies globally for both the overall SNAP trial and the pediatric cohort, SNAP-PY. This large-scale, collaborative Bayesian adaptive platform infrastructure is considered a cost-

 effective research investment that will inform clinical practice, which funding bodies have

 recognized and are willing to invest in.

Conclusion

It is evident there is an ongoing journey from the declaration by Harry Shirkey in 1963 that children were “therapeutic orphans” to the vision by Halpern and colleagues of “no child left behind” in clinical trials. The paternalistic attempt to protect children from research risk has conversely caused harm by preventing children from benefiting from clinical trial evidence to improve their health outcomes. The SNAP trial provides an example of a Bayesian adaptive whole-of-life inclusion design. Age-based exclusion of participants in the future may increasingly be viewed as unethical and unjustifiable. A new level of learning will arise from trial data analysed across a broader age range. This model will enhance trial population inclusion diversity overall, as well as generalisability, and has the potential to accelerate the translation of findings into clinical practice. SNAP and SNAP-PY have facilitated a strong international network of adult and pediatric clinician-researchers and statistical expertise focused on improving infection management across the life course. This model provides a pathway for addressing barriers to gaining timely high-quality pediatric evidence and may in the future be applied to trials of other priority and emerging diseases.

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Table 1 Secondary trial endpoints for the pediatric arm of the trial, *S. aureus* Network Adaptive Platform - Pediatric and Youth (SNAP-PY)

(For the primary and secondary SNAP overall trial endpoints see <https://www.snaptrial.com.au/>, NCT05137119)9.

|  |
| --- |
| **Secondary SNAP-PY trial endpoints that are pediatric-specific** |
| An additional pediatric composite endpoint will comprise of four existing core secondary endpoints from the SNAP trial;1. Microbiological treatment failure (Positive sterile site culture for *S. aureus* [of the same silo as the index isolate] between 14 and 90 days after platform entry)
2. Diagnosis of new foci between 14 and 90 days after platform entry
3. Mortality by 90 days following platform entry
4. Length of total index hospitalisation of >30 days from platform entry. Total index hospitalisation is defined as a continuous admission to any healthcare facility, including rehabilitation hospitals, hospital-in-the-home or outpatient parental antibiotic therapy services.

These endpoints have been shown to be useful outcome measures in children based on the ISAIAH study29. If an event is observed in any of the four endpoints, then the composite endpoint will be considered to have been met. |

Figure 1. Examples of three distinct clinical trial design strategies to incorporate children into clinical trials: sequential, parallel and unified adult-pediatric Bayesian adaptive design



Supplementary appendix 1: Inclusion and exclusion criteria for the *S. aureus* Network Adaptive Platform (SNAP) trial

|  |  |
| --- | --- |
| Inclusion criteria | Exclusion criteria |
| 1. Staphylococcus aureus complex grown from ≥1 blood culture 2. Admitted to a participating hospital at the time of eligibility assessment | 1. Time of anticipated platform entry is greater than 72 hours post collection of the index bloodCulture2. Polymicrobial bacteraemia, defined as more than one organism (at species level) in the indexblood cultures, excluding those organisms judged to be contaminants by either the microbiology laboratory or treating clinician3. Patient currently being treated with a systemic antibacterial agent that cannot be ceased (unless antibiotic is listed in Table 1, of the SNAP trial protocol, which specifies allowed antibiotics with limited absorption from the gastrointestinal tract or negligible antimicrobial activity against *S. aureus*)4. Known previous participation in SNAP5. Known positive blood culture for S. aureus (of the same silo: PSSA, MSSA or MRSA) between 72 hours and 180 days prior to the time of eligibility assessment6. Treating team deems enrolment in the study is not in the best interest of the patient7. Treating team believes that death is imminent and inevitable8. Patient is for end-of-life care and antibiotic treatment is considered not appropriate9. Patient <18 years of age and pediatric recruitment not approved at recruiting site |

Abbreviations: PSSA; penicillin susceptible *S. aureus*, MSSA; methicillin susceptible *S. aureus*, MRSA; methicillin resistant *S. aureus;* SNAP; *S. aureus* Network Adaptive Platform trial

 Supplementary Appendix 2 *S. aureus* Network Adaptive Platform (SNAP) trial design

**Abbreviations: EOS; early oral switch, IV; intravenous, PSSA; penicillin susceptible *S. aureus*, MSSA; methicillin susceptible *S. aureus*, MRSA; methicillin resistant *S. aureus*

Supplementary appendix 3 *S. aureus* Network Adaptive Platform (SNAP) trial overview of initial trial design interventions (domains) according to *S. aureus* antimicrobial susceptibility profile (silos)

|  |  |  |  |
| --- | --- | --- | --- |
| **Silo** | **Antibiotic Backbone Domain** | **Adjunctive Treatment Domain** | **Early Oral Switch Domain** |
| ***PSSA*** |  (Flu)cloxacillin\*Penicillin | No clindamycin\* vsClindamycin | Usual care\* (*initial 2-6 week antibiotic backbone treatment course given intravenously*) versus early oral switch algorithm (*as detailed in the relevant DSA*) |
| ***MSSA*** |  (Flu)cloxacillin\*Cefazolin |
| ***MRSA*** | Vancomycin/Daptomycin\* vsVancomycin/Daptomycin plus cefazolin |

Note that domains and interventions may be added or dropped during the life of the platform. This initial design is given only as an illustration of the trial’s structure.

\*=Comparator/control group

Abbreviations: PSSA; penicillin susceptible *S. aureus*, MSSA; methicillin susceptible *S. aureus*, MRSA; methicillin resistant *S. aureus*

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