Letter to the Editor

Comparators, consent, equipoise and estimands: ethical trade-offs in neonatal pain trials

Luke Baxter, Maria M. Cobo, Rebeccah Slater

Department of Paediatrics, University of Oxford, Oxford, UK

Correspondence to: Professor Rebeccah Slater, PhD, MSc, BSc, MA (Oxon), ARCS. Department of Paediatrics, University of Oxford, Oxford, UK. Email: rebeccah.slater@paediatrics.ox.ac.uk.

Response to: Harrison D, Bueno M. Ethics of trial of effect of parental touch on relieving acute procedural pain in neonates. Transl Pediatr 2024;13:1909-12.

Morris BJ. Parental participation in neonatal heel lance pain management. Transl Pediatr 2024;13:1294-301.

Submitted Jan 29, 2026. Accepted for publication Mar 31, 2026. Published online Apr 28, 2026.

doi: 10.21037/tp-2026-1-0110

View this article at: https://dx.doi.org/10.21037/tp-2026-1-0110

The generation of new medical knowledge in neonates, including research on pain-reduction strategies, requires well-designed and rigorously conducted clinical trials that are grounded in fundamental ethical principles. These principles include considering the scientific and social value, equipoise, and the attainment of fully informed consent—despite the inherent challenges of surrogate decision-making (1,2).

An example of such research is the Petal trial, a family-centred, add-on study in which baseline comfort measures were provided in both study arms, and the randomised contrast concerned the timing of an additional parental-touch intervention (3,4). In this pragmatically designed trial, participation did not restrict access to clinically appropriate analgesic strategies or requested comfort; rather, parents and clinicians were free to use additional measures in accordance with local practice.

A key design feature of pragmatic add-on trials, such as the Petal trial, is that—rather than withholding evidence-supported analgesia, which would require exceptionally strong ethical justification—they evaluate the incremental benefit of an intervention relative to a defined baseline level of analgesic provision. Two important ethical considerations are whether the baseline analgesic provision is adequate, and whether the design answers the intended scientific question (3). Here, "adequate" means a baseline that is evidence-based and routinely delivered to the eligible population, without changing the trial's estimand (the treatment effect that the clinical trial aims to estimate) into a fundamentally different measure.

This debate is best understood in terms of linked trade-offs. Best practice guidance on control-group selection emphasises that the choice of comparator depends on the research question, feasibility, and intended inference (5). In pragmatic neonatal pain trials, at least four questions need to be considered together: (I) the estimand, (II) the baseline analgesic provision that is feasible for all participants; (III) the handling and reporting of co-interventions; (IV) and consent disclosure regarding realistically available alternatives (5).

Usual care and "best evidence"

Harrison and Bueno argue that defining "usual care" by local practice (swaddling and non-nutritive sucking in the Petal trial sites) is problematic when breastfeeding, skin-to-skin care, and sweet solutions are evidence-based and recommended, and in their view, should be a fundamental component of "usual care" in neonatal pain studies (1). To consider this argument, it may help to separate two propositions: (I) neonates should receive the best achievable pain care in routine practice, and (II) groups in every trial must embed an idealised "best-evidence" bundle. The first is a normative ethical claim; the second is a methodological choice that can change the estimand and potentially undermine the motivating research question. Trial guidance recognises that different control groups serve different purposes, and that adding background therapies and co-interventions can change interpretability (5).

An alternative to enforcing an idealised "best evidence"

bundle in all groups is to explicitly describe the ethical baseline: define what every infant receives, ensure it is evidence-based, routinely deliverable, and feasible for all participants, and report co-interventions transparently. Methodological work on "usual care" comparators highlights why this issue is so important: usual care is often heterogeneous and poorly specified. While standardisation can improve internal validity (the degree to which observed effects can be causally attributed to the intervention rather than bias or confounding), it may reduce external validity (the extent to which trial findings are generalisable to real-world settings), requiring trialists to justify the resulting trade-off (6). Uptake and implementation of recommended neonatal pain strategies is variable, which is why pragmatic trials comparing 'add-on interventions' with 'usual care' are so frequently proposed.

Including sucrose in "usual care"'

A common discussion in neonatal pain research related to the definition of "usual care" concerns the use of sucrose. The Petal trial did not provide a detailed discussion of key systematic reviews evaluating the effectiveness of sweet solutions in reducing neonatal pain because, although this literature is important, sucrose represents a single intervention rather than a gold standard of care. Ethical questions cannot be resolved by citation completeness alone. They are more directly addressed by specifying what "effective analgesia" means when different endpoints are used to assess effectiveness. Because pain is subjective and there is no gold-standard measure in non-verbal infants, behavioural, physiological, and neurophysiological measures serve as proxies. Cochrane evidence suggests that sucrose, versus placebo or no intervention, reduces behaviourally-focussed pain scores after a single heel lance (7). Yet sucrose can reduce behavioural scores without altering other neural pain proxies, implying dissociable outcome constructs (8). This does not negate the ethical value of reducing behavioural distress through the use of sucrose, but it does mean behavioural benefit alone should not determine the endpoint for every trial. In Petal, where the primary endpoint is an EEG-derived response, this distinction shapes the evidence that is used to select the relevant estimand (3).

Equipoise: where the hardest line belongs

Harrison and Bueno's equipoise argument is strongest when directed at study designs that knowingly expose infants to avoidable pain by withholding feasible, evidence-supported analgesia. This is not the case in the Petal trial (1). Clinical equipoise concerns genuine uncertainty within the expert clinical community about the comparative merits of interventions under study (9). When effective analgesia is feasible and can be provided without undermining the research question, the ethical bar for placebo or non-treatment controls is rightly extremely high (5). In pragmatic add-on trials, however, equipoise may instead concern the incremental intervention itself, provided an ethical baseline of appropriate care is maintained and described (5,9). The aim is to align the comparator with the research question, while ensuring a clinically defensible approach (such as the use of swaddling and non-nutritive sucking) that does not permit avoidable undertreatment.

Consent, disclosure, and preserving the scientific question

The commentary also asks whether consent is "fully informed" if parents are not told about effective alternatives, and, in this specific example, whether parents could hold their babies rather than stroke their baby's leg (1). This question is relevant given that empirical data shows persistent challenges in neonatal trial consent: timing constraints, parental stress, and variable comprehension can limit what "full information" means (10). An appropriate strategy is to standardise disclosure around what is available and requestable in a particular setting: the baseline comfort measures provided to all infants, any additional options routinely available locally (and the practical conditions for using them), what parents can request or pursue as part of usual clinical care, and what the trial intervention adds. This may mitigate equity concerns without turning informed consent into a co-intervention that changes the scientific question.

Implementation gaps and the role of pragmatic trials

Harrison and Bueno argue that neonatal pain management practices have changed very little over decades, and that responsibility should shift towards system-level implementation strategies (1). This aligns with broader reviews of neonatal procedural pain epidemiology and treatment trends (11). However, it is more appropriate and

constructive to avoid framing this as a binary choice between "more trials" or better "implementation strategies", and instead to assess the value of both. Pragmatic trials can form part of an implementation pathway when they address decision-relevant questions in settings where uptake is heterogeneous and feasibility constraints matter. In that sense, the ethical case for some pragmatic trials may be strengthened, rather than weakened, by implementation gaps.

Cessation, gatekeeping, and governance

The commentary calls "*for cessation of newborn pain trials where sick and healthy newborns do not receive the best evidence*", and explicitly recommends cessation of trials that include (I) a placebo or non-treatment arm, or (II) omit breastfeeding or skin-to-skin (when feasible), or administration of sweet solutions. However, such calls for cessation risk being too blunt, if they preclude pragmatic studies that are needed to shift practice in some contexts, for example, where implementation lags behind generation of new scientific knowledge.

It may help to separate governance from norm-setting. Trials such as the Petal trial proceed within formal ethical review, monitoring arrangements, and protocol transparency requirements (3). Ethics approval is necessary, but it does not resolve the normative debate about optimal standard care and comparators; rather, it signals that such questions are contestable and subject to formal oversight. Disagreements are therefore best framed as opportunities to refine standards and review criteria, rather than as implicit indictments of investigator intent or diligence. Norm-setting may be most productive when it encourages explicit baselines, transparent co-intervention capture, and estimand clarity, rather than relying on a single "best-evidence baseline" rule as the decisive gate. This could be interpreted as discouraging research in settings where implementation lags, even when the trial's purpose is to help close that gap.

In closing, ethics in neonatal pain research is not only about maximising analgesia as "usual care"; it is also about ensuring that trials answer the relevant question with enough validity to justify asking families to participate.

Acknowledgments

None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office *Translational Pediatrics*. The article did not undergo external peer review.

Funding: None.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-2026-1-0110/coif). R.S. reports grants from Wellcome, European Institute of Innovation and Technology (EIT), Medical and Life Sciences Translational Fund (MLSTF)—University of Oxford, and consulting fees from Reckitt and Cooper Consumer Health. These conflicts are not directly related to the manuscript. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Harrison D, Bueno M. Ethics of trial of effect of parental touch on relieving acute procedural pain in neonates. Transl Pediatr 2024;13:1909-12.
2. Eccleston C, Fisher E, Howard RF, et al. Delivering transformative action in paediatric pain: a Lancet Child & Adolescent Health Commission. Lancet Child Adolesc Health 2021;5:47-87.
3. Hauck AGV, van der Vaart M, Adams E, et al. Effect of parental touch on relieving acute procedural pain in neonates and parental anxiety (Petal): a multicentre,

randomised controlled trial in the UK. Lancet Child Adolesc Health 2024;8:259-69.
4. Morris BJ. Parental participation in neonatal heel lance pain management. Transl Pediatr 2024;13:1294-301.
5. International Council for Harmonisation (ICH). E10: Choice of Control Group and Related Issues in Clinical Trials. 2000. Available online:
6. Turner KM, Huntley A, Yardley T, et al. Defining usual care comparators when designing pragmatic trials of complex health interventions: a methodology review. Trials 2024;25:117.
7. Yamada J, Bueno M, Santos L, et al. Sucrose analgesia for heel-lance procedures in neonates. Cochrane Database Syst Rev 2023;8:CD014806.
8. Slater R, Cornelissen L, Fabrizi L, et al. Oral sucrose as an analgesic drug for procedural pain in newborn infants: a randomised controlled trial. Lancet 2010;376:1225-32.
9. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987;317:141-5.
10. Wilman E, Megone C, Oliver S, et al. The ethical issues regarding consent to clinical trials with pre-term or sick neonates: a systematic review (framework synthesis) of the empirical research. Trials 2015;16:502.
11. Bueno M, Rao M, Aujla P, et al. A scoping review of the epidemiology and treatment of painful procedures in hospitalized neonates: What has changed in the past three decades? Eur J Pain 2024;28:1468-85.

Cite this article as: Baxter L, Cobo MM, Slater R. Comparators, consent, equipoise and estimands: ethical trade-offs in neonatal pain trials. Transl Pediatr 2026;15(4):162. doi: 10.21037/tp-2026-1-0110