Application of the Target Trial Emulation Framework to Studies in the Pediatric Population

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Children and adolescents often are excluded from randomized clinical trials (RCTs) that study the effect of medications, vaccines, or medical devices. Therefore, evidence must necessarily come from observational studies.[1,2] However, challenges exist when conducting a nonrandomized study, such as identifying a comparable reference group and defining the start of follow-up,[3-5] and studies in the pediatric population present unique additional methodologic challenges.

Conceptualizing an observational study as an emulation of a hypothetical RCT can help avoid common methodologic pitfalls such as prevalent user bias,[6,7] immortal time bias from the misalignment of time zero,[4,8,9] and selection bias.[4] Nonetheless, few pediatric studies to date have applied this framework (**Figure**). In this commentary, we discuss how to implement the target trial emulation framework in pediatric research and outline key pediatric-specific considerations.

What Is the Target Trial Emulation Framework?

The target trial emulation framework[10,11] provides a structured approach to designing and implementing nonrandomized studies of medical interventions and involves a 2-step process. Key terms in quotes are defined in **Appendix Table 1** (available at www.jpeds.com). First, investigators define an explicit research question, one that is transparent about the "causal estimand" of interest, and conceptualize a hypothetical "pragmatic trial" to answer this question (the "target trial"). This hypothetical trial should be conceptualized as a pragmatic trial. Blinded, placebo-controlled trials do not reflect clinical practice and cannot be emulated in real-world data.[12,13] Moreover, the data source needs to be fit for the research questions.[14] For instance, a pediatric trial with a symptom-based outcome could not be emulated within a data source that does not adequately capture this information.

Once a plausible target trial has been conceptualized, the details should be explicitly outlined as described in the Transparent Reporting of Observational Studies Emulating a Target Trial (TARGET) guideline.[15] The description should also include relevant elements of trial design that are specific to the pediatric population, such as details on weight-based dosing and pediatric-specific outcome definitions, as applicable. The target trial does not necessarily need to be feasible, as this is a guiding framework, but the treatment strategies should be identifiable, and deviations from what occurs in clinical practice should be justifiable. For example, it is possible to justify a hypothetical trial that is not restricted to children with a treatment indication (ie, without equipoise), if the investigators can defend that the groups compared are "exchangeable" regarding their risk for the outcome of interest (eg, a hypothetical trial comparing short-term use of ibuprofen vs no ibuprofen [without requiring an indication] on the risk of gastrointestinal bleeding, as the indication for ibuprofen generally does not impact gastrointestinal bleeding).

Second, this study design should be emulated as closely as possible using observational data. Ideally, specifications of the emulation should be the same as the target trial, aside from randomization. Deviations from the target trial protocol can be explicitly identified to expose the assumptions needed to obtain valid estimates. Pre-registration of a date-stamped study protocol before the start of data analysis is best practice for improving transparency.[16]

Application Example in the Pediatric Population

To describe the steps of the target trial framework and highlight pediatric-specific considerations, we outline the protocol of a hypothetical pragmatic trial to compare the effect of initiating and continuing carbamazepine vs lamotrigine vs oxcarbazepine vs valproate (for any indication) on the risk of developing type 2 diabetes (T2D) over a 5-year period in a sample of children and adolescents aged 10-18 years without diabetes and describe the emulation of the target trial

RCT	Randomized controlled trial
T2D	Type 2 diabetes

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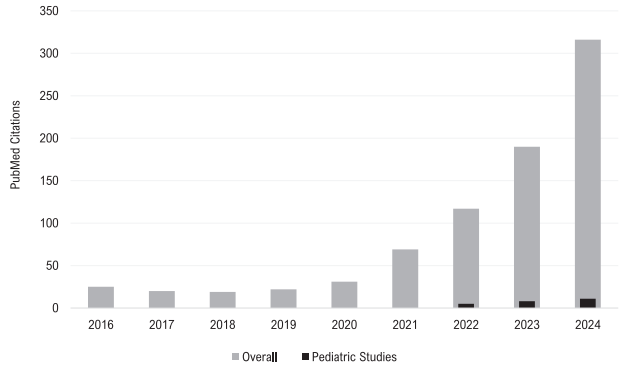

Figure 1. Number of PubMed citations for the "target trial" framework, 2016-2024. Overall counts determined on the basis of a PubMed search for the term "target trial." Number of pediatric studies capture the subset of target trial studies that include the pediatric population.

within claims data (on the basis of a previously published study).[17] Target trial specifications and the emulation in claims data are detailed in Table I, and the key pediatric-specific considerations in each step are described to follow.

Eligibility Criteria

Target Trial. Several pediatric-specific considerations exist when defining the eligibility criteria of the target trial. First, an appropriate age range should be selected on the basis of clinical indication and the availability (or lack) of existing rigorous, high-quality evidence across pediatric ages. In our application example (Table I), the age limit was chosen to include the population that is traditionally excluded from RCTs. Second, investigators should consider the "target population of interest," which includes determining whether the eligibility criteria should include restriction to the treatment indication. Many medications are used off-label in children.[20,21] Including the reason someone receives treatment as an inclusion criterion could make the treatment groups more comparable, but it could also impact the generalizability of the findings to those with other indications.

Emulation. The emulation should include definitions developed specifically for use in the pediatric population to define the eligibility criteria when available. For example, diagnosis codes for pediatric body mass index (as opposed to adult body mass index) should be used if obesity is an eligibility criterion in the target trial. Use of an active comparator (eg, lamotrigine) can increase the comparability between treatment groups, especially when the indication is poorly recorded in the data source (ie, restriction to indication cannot be emulated) or not specified (ie, indication not specified in the target trial) or when the target population of interest includes children who receive treatment on an off-label basis.[22,23] In our application example (Table I), a diagnosis of a treatment indication was required in the target trial, but evidence of a treatment indication was not required for inclusion in the emulation because medical diagnoses for chronic conditions are often under-recorded in claims data (ie, absence of a recorded diagnosis does not necessarily signify absence of the condition; eg, migraine), and the medications studied have limited treatment indications in clinical practice.

Treatment Strategies

Target Trial. An ideal RCT would generally assign a dosage on the basis of a child's age, underlying indication, and weight. However, weight and indication may be incompletely captured in observational databases, so weight-based and indication-based treatment cannot always be emulated. The target trial (such as the one described in Table I) is often a modification of that ideal RCT, one that can be emulated. A more realistic target trial could assign the dose by age and otherwise allow dosing "as clinically indicated," assuming that patients in real life receive the dosing recommended in the product label (eg, 100 mg twice a day for a child ≤12 years old with epilepsy initiating carbamazepine).

Emulation. The emulation should specify how the treatment intervention will be operationalized in observational data, including relevant information on dosing and formulation. When data on weight are not available in the data source used in target trial emulation, weight-based dosing cannot be included in its emulation (Table I). If dosing or formulation were relevant for the effect estimates, findings would correspond to the clinical practice in the source population.

Assignment Procedures

Target Trial. This specification describes a form of random assignment at enrollment that defines time zero.

Emulation. In the absence of randomization, adjustment for baseline confounding is needed because initiation of a treatment strategy may be triggered by clinical conditions that are also associated with the outcome. This confounding by indication poses one of the biggest threats to internal validity in nonrandomized studies. The list of potential confounders and operational definitions should be pediatric-specific, as the relevant confounders may differ from those that would be included in an analogous adult study.[24] For example, statins are associated with an increased risk of T2D and may be a potential confounder in an adult study,[25] but the prevalence of statin use in children is low,[26] so it may not be a relevant confounder in a pediatric study of antiseizure medications and risk of T2D.

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Table I. Target trial specification and emulation in a health care claims database: example in antiseizure medications and risk of developing type 2 diabetes

Protocol components	Target trial	Emulation
Eligibility criteria	• Age 10-18 years at enrollment • Have an indication for treatment (epilepsy, bipolar disorder, migraine, neuropathic pain) • No use of an antiseizure medication in the previous year • No previous diagnosis of diabetes	Same as the target trial, except: • A recorded diagnosis for treatment indication is not required because medical diagnoses for chronic conditions are often under-recorded in claims data (ie, absence of a recorded diagnosis does not necessarily signify absence of the condition), and the medications studied have limited treatment indications in clinical practice* • Continuous insurance coverage in the previous year required to enable complete capture of information in the claims data* Defined using enrollment data, outpatient dispensing data, diagnosis codes, and procedure codes in the claims
Treatment strategies	Initiation and continuation over 5 years of carbamazepine, lamotrigine, oxcarbazepine, or valproate Weight- or indication-based dose was not included in the target trial, nor its emulation, because of incomplete capture of weight and indications	Same as the target trial Treatment strategies classified based on outpatient medical dispensing Treatment adherence determined using a treatment diary constructed by dispensing dates and days' supply for each medication, with adherence operationally defined as the proportion of days covered ≥80%.
Assignment procedures	Children would be randomized to initiate a treatment strategy at enrollment	Children assigned to each treatment strategy are assumed to be comparable conditional on measured baseline covariates To emulate randomization, the target trial emulation will adjust for potential confounders measured during the year before baseline, including demographics, treatment indications, metabolic conditions, psychiatric conditions, lifestyle factors, other medications dispensed, and health care use as proxies of potential confounders that may be hard to measure using claims data
Follow-up Period	The follow-up period begins once all eligibility criteria are met and the treatment is assigned† Children would be followed for up to 5 years after enrollment or until the onset of the outcome, death, or trial dropout	Same as the target trial Trial dropout emulated as the end of continuous enrollment in the claims
Outcome	Incident type 2 diabetes during follow-up	Same as the target trial Cases identified via a claims-based algorithm developed and validated specifically for the pediatric population‡,§
Causal contrasts of interest	Intention-to-treat effect (the effect of treatment initiation) Per-protocol effect (the effect of adherence to the assigned treatment strategy)	Observational analog
Analytic plan	Intention-to-treat analysis: Estimate 5-year risk of type 2 diabetes for initiation of each treatment strategy, with adjustment for loss to follow-up using predictors of censoring and the outcome¶ Per-protocol analysis: Estimate 5-year risk of type 2 diabetes for continuous use of each treatment strategy (censoring at the time of nonadherence), with adjustment for loss to follow-up (as described in the intention-to-treat analysis) and additional adjustment for predictors of adherence and the outcome Potential selection bias as the result of censoring at the time of treatment nonadherence would be accounted for using analyses¶	Same as the target trial, except with the additional adjustment for baseline confounding Apply inverse probability of treatment weights (IPTW) by using multinomial logistic regression conditional on baseline covariates to estimate stabilized weights Survival curves and absolute risks will additionally be weighted by IPTW to estimate confounding-adjusted estimates

*This component of the emulation could also be part of a target trial that identifies potential participants using information from an observational database.
†The selected follow-up period should consider the expected time between treatment and onset of the outcome (induction period). The definition of the causal estimand of interest would need to specify the interpretation of competing events, such as death.
‡This component of the emulation could also be part of a target trial that identifies outcomes using information from an observational database.
§Example of a pediatric-specific outcome for type 2 diabetes for the emulation: Teltsch et al.[18]
¶Details on how to implement the analytic approaches and generate survival curves are described elsewhere, in Murray et al.[19]

Follow-Up Period

Target Trial. The follow-up period begins once all eligibility criteria are met and the treatment is assigned, as detailed in Table I.

Emulation. Treatment initiation, achievement of eligibility, and start of follow-up need to be aligned to avoid introducing immortal time bias. This is especially important in studies of infants and neonates, as further described below. By considering interventions

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Table II. Example treatment strategies and implementation in the target trial framework

Treatment strategy	Example	Implementation in the target trial framework*
Initiation	Initiation of carbamazepine, lamotrigine, oxcarbazepine, or valproate (as per the application example)	Intention-to-treat effect (as per the application example in **Table I**) • Define the treatment strategy as initiation of treatment
Adherence	Continuation over 5 years of carbamazepine, lamotrigine, oxcarbazepine, or valproate; no allowable deviations (as per the application example)	Per-protocol effect (as per the application example in **Table I**) • Define the treatment strategy as adherence to the assigned medication during follow-up (eg, daily adherence to the assigned medication) • Adjust for potential selection bias due to censoring at the time of treatment nonadherence or discontinuation
Adherence, with allowable deviations specified in the treatment protocol	Continuation over 5 years of carbamazepine, lamotrigine, oxcarbazepine, or valproate Nonadherence due to an adverse event or contraindication are allowable deviations within the specified protocol	Per-protocol effect (with allowable deviations) • Define the treatment strategy as adherence to the assigned medication during follow-up (eg, daily adherence to the assigned medication) • Specify if any allowable deviations are within the treatment protocol (eg, nonadherence to the medication due to an adverse effect is still in adherence to the treatment protocol; therefore, lack of treatment adherence may not necessarily mean lack of adherence to the specified treatment protocol) • Adjust for potential selection bias due to censoring at the time of treatment nonadherence or discontinuation
Treatment duration comparison	Initiation of fluticasone for asthma treatment and using it for: <1 year vs 1-2 years vs >2 years	Clone-censor-weighting (details described elsewhere[31–33]) • Define the treatment strategy as a comparison between different treatment durations • Assign a "clone" each treatment strategy*(This step is needed because treatment groups are defined based on observed treatment duration, and during this time, the outcome can occur)* • Begin follow-up at the time of treatment initiation • Artificially censor the "clones" when they deviate from the treatment strategy • Apply weighting techniques to adjust for potential bias due to artificial censoring
Add-on therapy	When there is a lack of asthma symptom control within 4 weeks, add additional medication (step up)	Dynamic treatment strategy (details described elsewhere[29,30]) • Define the medications for initial treatment (eg, as-needed inhaled short-acting beta2-agonist for asthma treatment) • Define the new add-on treatments (eg, following the stepwise approach for asthma management) • Specify a rule for when the new treatment will be added to the initial treatment (eg, at the first instance of a treatment failure or lack of symptom control, add additional medication) • Adjust for potential time-varying confounding due to applying a dynamic treatment strategy(This step is needed because future treatment assignment during follow-up is determined by a patient characteristic [eg, the variable that defines "treatment failure"] that may also be associated with the outcome)
Treatment switching	After 4 weeks without improvement of depressive symptoms, switch to a different antidepressant medication	Dynamic treatment strategy (details described elsewhere[29,30]) • Define the medications for initial treatment • Define the new treatments that patients could switch to • Specify a rule for when the initial treatment will be discontinued and the new treatment will be initiated (eg, switch at the first instance of a treatment failure) • Adjust for potential time-varying confounding due to applying a dynamic treatment strategy(This step is needed because future treatment assignment during follow-up is determined by a patient characteristic [eg, the variable that defines "treatment failure"] that may also be associated with the outcome)
Deprescribing or discontinuation	At first improvement of symptoms for depression, reduce dose of antidepressant by 25%	Dynamic treatment strategy (details described elsewhere[29,30]) • Define the medications for initial treatment • Define the medication reduction (eg, dose reduction, discontinuation) • Specify a rule for when the initial treatment will be reduced (eg, after symptom improvement is sustained for 6 months) • Adjust for potential time-varying confounding due to applying a dynamic treatment strategy (This step is needed because future treatment assignment during follow-up is determined by a patient characteristic [e., the variable that led to treatment reduction] that may also be associated with the outcome)

*The target trial framework relies on selecting an appropriate analytic approach to answer the prespecified causal question of interest. These examples are not an exhaustive list of treatment strategies that may be of interest, and the appropriate implementation may differ on the basis of the specific question of interest. All scenarios should also consider adjustment for potential baseline confounding due to lack of randomization and potential selection bias due to loss to follow-up.

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Table III. Example sequential target trial specification to estimate the effect of initiating hypothetical treatment A on the risk of neonatal mortality in the first 4 weeks after birth

Protocol components	Target trial 1 (postnatal week 1, days 1-7)	Target trial 2 (postnatal week 2, days 8-14)	Target trial 3 (postnatal week 3, days 15-21)	Target trial 4 (postnatal week 4, days 22-28)
Eligibility criteria	Alive at birth (day 1)	Alive at day 8 after birth No previous use of treatment A at day 8 after birth	Alive at day 15 after birth No previous use of treatment A at day 15 after birth	Alive at day 22 after birth No previous use of treatment A at day 22 after birth
Treatment strategies	1) Initiate treatment A between birth (day 1) and day 7 after birth (end of postnatal week 1) 2) Do not initiate treatment A between birth (day 1) and day 7 after birth	1) Initiate treatment A between day 8 after birth and day 14 after birth (end of postnatal week 2) 2) Do not initiate treatment A day 8 after birth and day 14 after birth	1) Initiate treatment A between day 15 after birth and day 21 after birth (end of postnatal week 3) 2) Do not initiate treatment A day 15 after birth and day 21 after birth	1) Initiate treatment A between day 22 after birth and day 28 after birth (end of postnatal week 4) 2) Do not initiate treatment A day 22 after birth and day 28 after birth
Follow-up period	Start: Birth (day 1) End: Day 28 after birth (end of postnatal week 4) or loss to follow-up	Start: Day 8 after birth End: Day 28 after birth (end of postnatal week 4) or loss to follow-up	Start: Day 15 after birth End: Day 28 after birth (end of postnatal week 4) or loss to follow-up	Start: Day 22 after birth End: Day 28 after birth (end of postnatal week 4) or loss to follow-up
Outcome	Neonatal mortality	Neonatal mortality	Neonatal mortality	Neonatal mortality
Causal contrasts of interest	Effect of initiating treatment A between birth (day 1) and day 7 after birth compared to not initiating treatment A between birth (day 1) and day 7 after birth	Effect of initiating treatment A between day 8 after birth and day 14 after birth compared to not initiating treatment A between day 8 after birth and day 14 after birth	Effect of initiating treatment A between day 15 after birth and day 21 after birth compared to not initiating treatment A between day 15 after birth and day 21 after birth	Effect of initiating treatment A between day 22 after birth and day 28 after birth compared to not initiating treatment A between day 22 after birth and day 28 after birth

(eg, treatment initiation, discontinuation), prevalent user biases are avoided.[27]

Outcome

Target Trial. The outcome of the target trial should be detailed, as in Table I.

Emulation. When possible, an outcome definition (eg, a case-identifying algorithm within a health care database) specifically developed and validated for the pediatric population should be used. Outcome definitions developed for adults may not be appropriate for use in the pediatric population because the clinical presentation of the same outcome may differ in children and the same diagnosis code may not represent the same disease or disease severity. For example, a pediatric-specific outcome definition for T2D is needed to distinguish between type 1 diabetes and T2D (Table I). When an appropriate pediatric-specific case-identifying algorithm does not exist for the outcome of interest, investigators can develop and validate a new pediatric-specific outcome definition.[28]

Causal Contrasts of Interest

Target Trial. The application example (Table I) highlights the intention-to-treat and per protocol effects. The causal contrast of interest may vary by study.

Emulation. The emulation reflects the observational analog, as noted in Table I.

Analytic Plan

Target Trial. Additional subgroup analyses by age (eg, neonates, infants, children, adolescents) may be needed, given the differences in growth, development, disease course, and treatment effects across the pediatric population.

Emulation. Details on how to implement the analyses are described in Table I.[19]

Extending the Framework to Additional Treatment Scenarios

The target trial framework can be used to study additional treatment scenarios beyond the intention-to-treat and per-protocol effects described earlier. Table II summarizes select treatment strategies that often are studied in pediatric populations and highlights examples of how to implement them. For example, children may not continuously use treatment for the full duration of long-term follow up (eg, 5 years), so a dynamic treatment strategy that allows for adaptations when clinically indicated may provide a more realistic approach. Add-on therapies, treatment switching, and deprescribing can be incorporated as treatment strategies within the target trial

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framework as "dynamic treatment regimes."[29,30] Comparisons of treatment durations (eg, <1 year vs 1-2 years vs >2 years) can be studied using the "clone-censor-weighting" method to avoid introducing immortal time and selection biases.[31–33]

Extending the Framework to Address Immortal Time Bias in Studies of Neonates Plus Infants

Application of the target trial emulation framework prevents "immortal time bias" in studies of neonates and infants by aligning study eligibility achievement, treatment assignment, and the start of follow-up. In RCTs, the "time zero" is clearly defined for when the eligibility criteria are met, treatment strategies are assigned, and follow-up begins. In nonrandomized studies, misalignment of these aspects can create a window of time in the follow-up period when the outcome cannot occur, resulting in immortal time bias.[4,8] This is particularly common in nonrandomized studies of neonates and infants[34,35] because these studies often begin follow-up at birth, but the medical intervention of interest (eg, treatment, procedure, etc) occurs after birth only among those who survive long enough (and may be transferred to a suitable facility) to receive it. Therefore, the time from birth to the intervention is "immortal" to the outcome of interest.

To address this immortal time bias, the target trial framework can be extended to emulate a sequence of target trials. Instead of specifying 1 target trial, multiple target trials by week since birth can be specified. Balancing age at time zero is especially important because many end points change quickly over time as infants mature. Each week since birth would have its own target trial specification, with week-specific eligibility criteria, treatment strategies, and start of follow-up (ie, alignment of "time zero"), as well as week-specific causal contrasts of interest and corresponding effect estimates. Because each target trial captures a different age and includes a different follow-up time, the cumulative risks cannot be combined. Instead, relative risks from each week-specific target trial could be pooled to obtain 1 effect estimate. Additional details on implementation are published elsewhere.[36,37]

As an example, Table III specifies sequential target trials to address the question: What is the effect of initiating hypothetical treatment A on the risk of neonatal mortality in the first 4 weeks after birth? Four sequential target trials were specified, one for each week since birth. The specifications remain similar for each sequential target trial, but timing of the eligibility criteria, treatment strategies, and start of follow-up vary to ensure that time zero is aligned in each target trial.

Limitations

Application of the target trial framework does not solve all the challenges of nonrandomized studies. Even with the most rigorous methodology, some research questions cannot be addressed within observational data.[38] A fit-for-purpose data source that can capture the study population, interventions, outcomes, and patient characteristics must exist. A recent review of real-world data sources with pediatric populations found that most of the identified databases did not include information on weight,[39] which limits the ability to study treatment strategies that rely on weight but have wide pediatric dosing ranges. Similarly, symptoms or educational milestones are outcomes of interest in children, but these end points are often poorly captured in routinely collected health care databases. Despite the strengths of the target trial framework, some research questions with an exceptionally high risk of confounding may still be prone to residual bias even after adjustment for measured confounding factors. This may occur when data on key confounding factors are not well captured in the data source, resulting in substantial confounding due to unmeasured factors. In these cases, alternative approaches should be identified, including the conduct of an RCT.

Conclusions

The target trial emulation framework provides a structured approach to generating causal inferences from nonrandomized studies of clinical interventions that minimizes the avoidable biases in observational research, clarifies the research question of interest, and thus improves the validity and interpretability of findings. The process of designing the target trial and its emulation explicitly highlights the differences between the hypothetical trial and the emulation within observational data. Some of these differences, such as the lack of randomization, will apply to all observational studies. Other differences unique to the data source chosen for the emulation (eg, lack of weight in claims data) can be identified and addressed through the process of designing the target trial and its emulation. The exercise of explicitly specifying these steps in the study protocol can reveal potential pitfalls of the observational study, even when complete emulation of the target trial is not possible. Increased and appropriate uptake of the framework for nonrandomized studies in the pediatric population can improve the quality of evidence generated and lead to better informed treatment and policy decisions for children and adolescents. ■

CRediT authorship contribution statement

Jenny W. Sun: Writing – original draft, Methodology, Conceptualization. **Daniel B. Horton:** Writing – review & editing, Conceptualization. **Timothy J. Savage:** Writing – review & editing. **Mehmet Burcu:** Writing – review & editing, Conceptualization. **Sonia Hernandez-Diaz:** Writing – review & editing, Methodology.

Declaration of competing interest

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