

COMMENTARY

Specifying a target trial protocol to estimate the effect of preconception treatment of periodontitis on time-to-pregnancy: A commentary and applied example

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Abstract

Background: The target trial framework was developed as a strategy to design and analyze observational epidemiologic studies with the aim of reducing bias due to analytic decisions. It involves designing a hypothetical randomized trial to answer a question of interest and systematically considering how to use observational data to emulate each trial component.

Aims: The primary aim of this paper is to provide a detailed example of the application of the target trial framework to a research question in oral epidemiology.

Materials and Methods: We describe the development of a hypothetical target trial and emulation protocol to evaluate the effect of preconception periodontitis treatment on time-to-pregnancy. We leverage data from Pregnancy Study Online (PRESTO), a preconception cohort, to ground our example in existing observational data. We discuss the decision-making process for each trial component, as well as limitations encountered.

Results: Our target trial application revealed data limitations that precluded us from carrying out the proposed emulation. Implications for data quality are discussed and we provide recommendations for researchers interested in conducting trial emulations in the field of oral epidemiology.

Discussion: The target trial framework has the potential to improve the validity of observational research in oral health, when properly applied.

Conclusion: We encourage the broad adoption of the target trial framework to the field of observational oral health research and demonstrate its value as a tool to identify directions for future research.

KEYWORDS

epidemiology, observational studies, oral health, target trial emulation

1 | MOTIVATION FOR THIS COMMENTARY

The target trial framework provides a standardized method to explicitly state decisions about observational study design in order to

reduce investigator-induced bias.¹ Researchers specify a hypothetical target trial and use observational data to emulate this trial as closely as possible. Detailing the hypothetical trial clarifies study decisions, such as eligibility criteria and start of follow-up (i.e. time zero) and can reveal potential sources of bias. The use of the target

trial framework in observational research has proliferated in recent years, but the methodology is still relatively nascent. Our objective in this commentary is to detail the process of applying the target trial framework to an actual research question. By doing so, we aim to provide detailed recommendations and insights for research teams planning to use the target trial framework in observational research efforts, particularly in oral health.

2 | SCIENTIFIC BACKGROUND

Our target trial will estimate the effect of preconception periodontitis treatment on time to pregnancy (TTP). The rationale lies in the fact that many observational studies have identified an association between periodontitis during pregnancy and birth outcomes.² However, questions remain about whether this association is causal, as periodontitis treatment is not consistently associated with reductions in these outcomes. A Cochrane Review of 15 trials found no conclusive evidence of a benefit of treatment on pregnancy outcomes.³ One explanation for the lack of clear efficacy is that any putative causal mechanisms may be established before pregnancy and treatment during pregnancy may occur too late to influence outcomes.^{4,5} Indeed, recent studies specifically evaluating preconception periodontitis and reproductive outcomes have demonstrated that a self-reported history of periodontitis was associated with both a prolonged TTP and a higher risk of miscarriage.^{6,7}

To date, no clinical trials have evaluated preconception periodontitis treatment and reproductive outcomes. If preconception treatment trials were to demonstrate no effect on TTP, this may provide mechanistic insights into the relationship between periodontitis and reproductive outcomes more broadly. Preconception trials are challenging, however, because of ethical considerations, the high prevalence of unplanned pregnancies, the large study size required and competing events, including infertility and pregnancy loss.⁸ Observational research presents an opportunity to glean insights into preconception oral health but requires care to avoid biases. The target trial framework represents a potential strategy to enhance the validity of observational studies of preconception periodontitis treatment.⁹

In this commentary, we detail the development of a target trial protocol.¹ We build on prior research, which found an association between a preconception history of periodontitis and TTP⁶ and propose a target trial emulation evaluating the efficacy of preconception treatment of periodontitis on TTP using data from a preconception cohort study.¹⁰

3 | METHODS

3.1 | Data source

Designing a target trial within the context of an existing observational data source can help facilitate an effective emulation

because limitations of the data can be factored into the trial design. We designed our target trial protocol to be emulated using data from Pregnancy Study Online (PRESTO). PRESTO is an ongoing, web-based preconception cohort study that collects data from female participants attempting conception.¹⁰ Participants are recruited primarily using online methods, such as social media advertisements and health-related websites, in addition to traditional methods (e.g. posted flyers and word of mouth). Eligible participants identify as female, are aged 21–45 years, reside in the United States or Canada, are in a relationship with a male partner and are actively attempting pregnancy without fertility treatments. There is no restriction on duration of pregnancy attempts at enrolment.

At enrolment, participants complete a questionnaire that contains information about overall health, reproductive history and lifestyle factors. It also includes the following questions related to current oral health and oral health history, adapted from clinically validated self-report measures used for population surveillance of periodontitis^{11,12} and observational research¹³: 'Has a dentist or dental hygienist ever told you that you had periodontal or gum disease? (Yes/No/Don't Know),' and 'Have you ever had treatment for gum disease such as scaling and root planing, sometimes called 'deep cleaning'? (Yes/No/Don't Know).' Those who report a diagnosis or history of treatment also answer the following questions: 'Approximately how old were you when you were first told that you had periodontal or gum disease?', 'Approximately how old were you when you first had treatment for periodontal or gum disease (i.e. scaling and root planing, sometimes called 'deep cleaning')?' and 'Approximately how old were you at the time of your most recent treatment for gum disease (i.e. scaling and root planing, sometimes called 'deep cleaning')?' all of which had open-ended text forms for age in years. TTP is assessed via self-report using enrolment and follow-up questionnaires sent every 8 weeks after enrolment. On the enrolment questionnaire, participants reported their date of last menstrual period (LMP), usual cycle length (if they had regular menstrual cycles) and the number of cycles of conception attempts at cohort entry. On each follow-up questionnaire, participants reported their most recent LMP date and whether they had become pregnant since the previous questionnaire. Among those with irregular menstrual cycles, we estimated cycle length based on date of LMP at baseline and prospectively-reported LMP dates during follow-up. TTP was calculated as follows: menstrual cycles of attempt at study entry + [(LMP date from most recent follow-up questionnaire – date of baseline questionnaire completion)/usual menstrual cycle length] + 1.

Prior analyses using PRESTO data found an association between a preconception history of diagnosis of and, separately, treatment for periodontitis with prolonged TTP, compared with those with no history of periodontitis.⁶

The study protocol was reviewed and approved by the Boston University Medical Campus Institutional Review Board and participants provided informed consent online.

3.2 | Process for applying the target trial framework

3.2.1 | Developing a causal question

Target trial emulation requires the development of a clearly specified causal question that could be addressed with a trial. This is often an iterative process where the causal question is updated and respecified as details of the target trial and possible emulation plans are clarified. Before specifying the target trial, we first reviewed our broader scientific question and available data to identify a causal question of interest that could be answered using the data we had. We recommend that any research team planning a target trial conduct this process and consider describing it in any resulting manuscript.

Our broader scientific question was: 'Among females with periodontitis during the preconception period, how does receiving treatment for periodontitis affect TTP?' This question lacks the specificity of an ideal causal question. The latter is more properly expressed as a counterfactual: if the observed exposure A had actually been B, what would have happened to outcome Y? In order to answer this question, we need to specify precisely A, B and Y.^{14,15}

To define a periodontitis treatment strategy and meaningful comparator, we considered both type (e.g. non-surgical scaling and root planing vs surgery) and timing (e.g. continuous treatment compared with a single treatment). The target trial can accommodate the evaluation of a wide range of treatment strategies because there is no actual random assignment of treatments. Consequently, we can include data from participants who experience a treatment paradigm that would be unethical to assign in a trial, but that nonetheless occurs in the real world (e.g. a patient discontinuing necessary treatment due to financial constraints).

In a preconception cohort, there is heterogeneity in terms of when participants received treatment, were diagnosed with periodontitis, initiated conception attempts and enrolled in the cohort (visually depicted in Figure 1). A target trial could compare any of these treatment schemas, given sufficient detail and study sizes in a data source. Evaluating different patterns of treatment adherence (including patterns of discontinuation and incomplete adherence) can provide insights consistent with pragmatic trials.¹⁶ When considering treatment strategies, we evaluated the data available in PRESTO. We had limited data on treatment: only whether participants had ever received any treatment for periodontitis and, if so, the ages at their earliest and most recent treatment(s). Thus, our ability to emulate specific treatment strategies was limited, because we lack data on exactly what date the treatments occurred in relation to enrolment, the type of treatment or whether additional treatments occurred between the first and most recent treatments or after enrolment (see Figure 1 for more details). Because periodontitis is a chronic condition, management can be ongoing and include maintenance treatments.¹⁷ With more detailed data about treatment, we would specify specific treatment comparators of interest. For the purposes of this paper, we did not define specific treatment types for our causal question, but clearly specified treatment comparators would be necessary in an actual target trial emulation.

A causal question also benefits from specification of the relevant population in which a hypothetical trial would occur. Our broad scientific question of interest concerns 'preconception' treatment of periodontitis, but we needed to clarify this description. In general, the 'preconception' period is the time period before a person becomes pregnant. To facilitate recruitment, the PRESTO cohort operationalizes this definition as the period of time during which a person identifies as a 'pregnancy planner'; that is, someone attempting

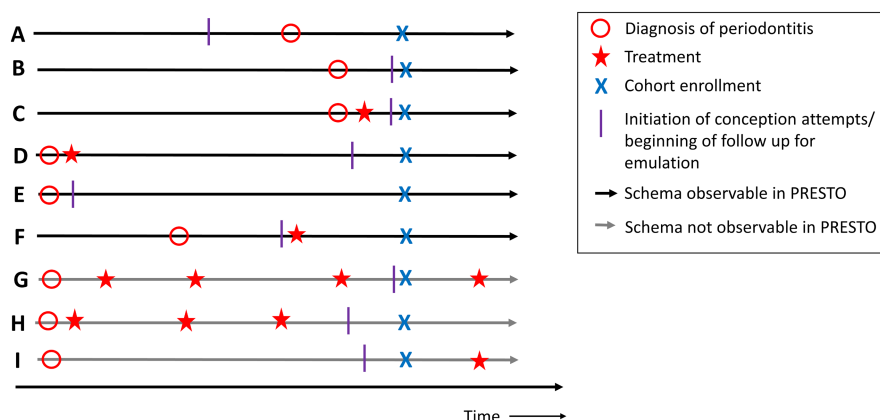


FIGURE 1 Depiction of example real-life treatment schemas and whether they are observable in PRESTO. (A) Diagnosis after initiation of conception attempts, no treatment; (B) Diagnosis proximal to initiation of conception attempts with no treatment, (C) Diagnosis and one treatment proximal to initiation of conception attempts, (D) Diagnosis and one treatment with a long period of no treatment before conception attempts, (E) Diagnosis proximal to initiation of conception attempts with a long lag before enrolment in cohort; (F) Diagnosis followed by initiation of conception attempts and then treatment, (G) Regular treatment beginning after diagnosis and continuing after enrolment, (H) Long-term, regular ongoing treatment since diagnosis, (I) Long lag time between diagnosis and initiation of conception attempts, first treatment received after cohort enrolment. Schemas A–F could be observed in PRESTO data, while schemas G–I could not. PRESTO, Pregnancy Study Online.

pregnancy but not yet pregnant. We chose to further define our population of interest as those who have been attempting pregnancy for no more than 6 cycles. We chose this definition because of the clinical relevance to new and recent pregnancy planners, as well as due to our lack of data on exact date of treatment. In addition, this definition helps reduce the possibility for reverse causation that could be observed with longer attempt times; since longer attempt times allows for more preconception time during which treatment can occur but may also reflect conception difficulties due to other causes (i.e. genetics).

This is not the only population of interest we could consider since there is heterogeneity in the duration of pregnancy attempts in any given preconception population. We could have chosen to consider a question relating to the extent to which treatment of periodontitis before any initiation of conception attempts affects TTP. Alternately, we could have chosen to consider a question about the efficacy of treatment among those with at least 6 cycles of unsuccessful attempts or a question about the effect of periodontitis treatment on TTP on a per-cycle basis, in which treatment is evaluated against no treatment at each cycle of conception attempts.

These decisions enabled us to hone our broader scientific question into a causal question to inform our target trial specification: 'Among females with diagnosed periodontitis who self-identify as pregnancy planners and have been attempting conception for no more than 6 cycles, would their TTP have been different if they had received treatment appropriate for their disease severity in the preconception period compared to if they had not received treatment during the preconception period?'

3.2.2 | Considering 'time zero'

With the causal question in mind, we considered the appropriate point to begin followup time (i.e. 'time zero'). In a randomized trial, follow up time begins with randomization. In an observational emulation, the specification of time zero can introduce myriad biases because of the interplay between treatment initiation and when a participant meets the specified eligibility criteria. This is particularly challenging when the comparison group of interest is receiving no treatment. Emulation failures related to misspecification of time zero are comprehensively detailed in Hernan et al, 2016.⁹ To reduce the opportunity for bias, time zero and treatment status should be specified at the time that individuals become eligible. When treatment can occur before time zero, the primary concerns are a change in the study population, which can occur when both eligibility and treatment occur before time zero, and selection bias, which can occur if treatment affects subsequent baseline eligibility. If treatment affects baseline eligibility, then collider stratification bias may occur if there are common causes of eligibility and the outcome. These biases can be mitigated by careful interpretation of study results and appropriate control for common causes of eligibility and the outcome. On the other hand, when treatment or eligibility can occur after time zero, the primary concern becomes immortal time bias. This bias is much more difficult to mitigate and requires both sufficient time-varying data and more complex statistical analyses.^{1,9}

In our case, the determination of time zero is made more complex because we must also consider the relationship between when participants initiated conception attempts and when they enrolled in PRESTO, as some individuals attempted conception for some time before enrolling in PRESTO. Figure 2 details three possible time zero

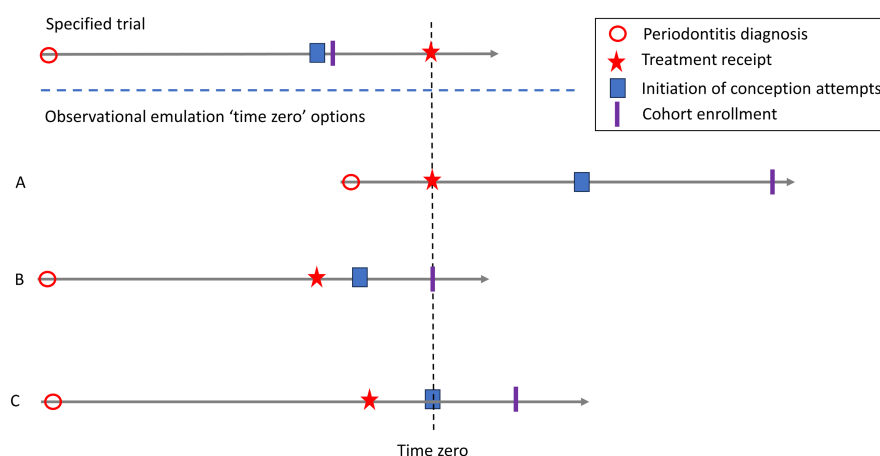


FIGURE 2 Depictions of our specified trial and time zero considerations in our trial emulation. d: (A) Time zero designated at treatment receipt, which occurs prior to initiation of conception attempts (eligibility) and enrolment. Person time which occurred after treatment but prior to the initiation of conception attempts, when couples may have been actively preventing pregnancy, would be analogous to inappropriate randomization in the specified trial, since those who are not pregnancy planners are not eligible for our study. Including these individuals could also induce immortal time bias. (B) Time zero designated at cohort enrolment, following both eligibility and treatment assignment. Follow up may be left truncated, discarding potentially useful information. This can cause bias in the effect estimate.⁹ In addition, the introduction of cohort eligibility criteria after treatment and initiation of conception attempts can potentially induce selection bias. This bias can be mitigated by analytic adjustment. (C) Time zero designated at initiation of conception attempts, after treatment receipt. This is the strategy we ultimately selected, with included bounds on the amount of time that could have elapsed between treatment receipt and initiation of conception attempts (12 months) due to the potential waning treatment effect.

designations we considered, as well as potential biases. Ultimately, we decided that the most appropriate 'time zero' was initiation of conception attempts (i.e. discontinuation of contraceptive or protection against pregnancy) because it posed the lowest risk of bias of the three possible time zero assignments. Assigning time zero at treatment receipt presented the potential for the inclusion of person time in which couples may have been preventing pregnancy and assigning time zero at cohort enrolment presents the risk of left truncation, which can bias effect estimates.⁹

3.2.3 | Identification of factors related to treatment receipt

Trial emulation attempts to emulate random assignment by adjusting for confounding factors related to the receipt of treatment and the outcome.¹ In this way, the emulation attempts to adjust for the elements in the real world that produce imbalance in the outcome across the study arms. This procedure can lead to residual confounding if randomization is incompletely emulated, that is, if not all confounding factors are adequately controlled. Trial emulation works best when the dataset contains information on a wide variety of characteristics at time zero.¹ Even with detailed covariate information, however, it is generally impossible to know whether trial emulations are biased due to uncontrolled confounding; approaches to assess the potential for unmeasured confounding are discussed in Hernán et al.¹

In the present example, it is necessary to adjust for covariates known to be related to having had periodontitis treatment. There are a few broad categories of factors potentially related to treatment receipt among those with a history of periodontitis: disease severity, socioeconomic status and access to dental care. To inform our emulation, we used PRESTO data to evaluate the distribution of characteristics, including factors potentially related to treatment receipt, among all PRESTO participants who reported a history of diagnosis of periodontitis ($N=677$) by whether they also reported receiving treatment (results displayed in Table 1).

3.3 | Target trial and emulation protocol

After finishing the iterative process through which we identified a causal question, we designed the trial and emulation. We followed the structure described in Hernán and Robins, 2016,¹ which identifies seven necessary components. Below, we specify each component for the target trial for emulation. The complete emulation is displayed in Table 2.

3.3.1 | Eligibility criteria

Target trial: Eligibility criteria include attempting pregnancy with one biologically male partner and having clinically-determined

TABLE 1 Descriptive comparison of characteristics potentially associated with receipt of treatment among those in PRESTO with a positive history of periodontitis diagnosis ($N=677$).

Characteristic	Participants reporting a history of periodontitis diagnosis ($N=286$)	Participants reporting a history of treatment for periodontitis ($N=391$)
Age, years, mean (sd)	32.0 (4.3)	32.4 (4.1)
Age at periodontitis diagnosis (mean)	26.0 (6.5)	27.3 (5.6)
Years between periodontitis diagnosis and enrolment (mean)	6.0 (5.5)	5.1 (5.0)
Body mass index (mean)	28.9 (8.4)	30.2 (8.6)
Parous, n (%)	124 (43.4%)	150 (38.4)
Income, USD		
<15 000	6 (2.1)	4 (1.0)
15 000-24 999	14 (4.9)	7 (1.8)
25 000-49 999	37 (12.9)	38 (9.7)
50 000-74 999	52 (18.2)	58 (14.8)
75 000-99 999	38 (13.3)	76 (19.4)
100 000-124 000	39 (13.6)	67 (17.1)
125 000-149 999	26 (9.1)	44 (11.3)
150 000-199 999	33 (11.5)	39 (10.0)
200 000+	36 (12.6)	51 (13.0)
Education, years		
<12	1 (0.4)	1 (0.3)
12	20 (7.0)	9 (2.3)
13-15	61 (21.3)	70 (17.9)
16	82 (28.7)	120 (30.7)
≥17	122 (42.7)	191 (48.9)
Currently has dental insurance, %	245 (85.7)	354 (90.5)
Sugar sweetened beverage consumption		
0 servings/week	97 (34.0)	152 (39.0)
1 serving/week	45 (15.8)	54 (13.9)
2-6 serving/week	83 (29.1)	132 (33.9)
≥7 serving/week	60 (21.1)	52 (13.3)
Cigarette smoking status		
Never	229 (80.1)	300 (76.7)
Former	30 (10.5)	58 (14.8)
Occasional	8 (2.8)	13 (3.3)
Regular	19 (6.6)	20 (5.1)
Diabetes, n (%)	13 (4.6)	14 (3.6)
History of tooth mobility, n(%)	22 (7.8)	28 (7.2)
Currently employed, n(%)	245 (85.7)	346 (88.5)
Geographic region		
Northeastern U.S.	56 (19.6)	81 (20.7)

(Continues)

TABLE 1 (Continued)

Characteristic	Participants reporting a history of periodontitis diagnosis (N = 286)	Participants reporting a history of treatment for periodontitis (N = 391)
Southern U.S.	72 (25.2)	106 (27.1)
Midwestern U.S.	71 (24.8)	76 (19.4)
Western U.S.	48 (16.8)	87 (22.3)
Canada	39 (13.6)	41 (10.5)
Time since last visited a dentist for any reason		
Within last year	188 (65.7)	294 (75.2)
1–2 years	64 (22.4)	76 (19.4)
3–4 years	19 (6.6)	16 (4.1)
≥5 years	15 (5.2)	5 (1.3)
Time since last dental cleaning		
Within last year	167 (58.4)	288 (73.7)
1–2 years	66 (23.1)	76 (19.4)
3–4 years	22 (7.7)	18 (4.6)
≥5 years	31 (10.8)	9 (2.3)
Rate the health of your teeth and gums		
Excellent	16 (5.6)	17 (4.4)
Very good	79 (27.6)	101 (25.8)
Good	89 (31.1)	162 (41.4)
Fair	74 (25.9)	91 (23.3)
Poor	28 (9.8)	20 (5.1)

Abbreviations: PRESTO, Pregnancy Study Online; sd, standard deviation; U.S., United States; USD, United States Dollars.

periodontitis, assessed by trained clinicians using an established operational definition. Exclusion criteria includes being pregnant and using fertility treatment or contraception. We additionally restrict participants to ≤6 cycles of conception attempts at enrolment, with planned sensitivity analyses to explore the potential for duration of pregnancy attempt time to act as a modifier (i.e. a secondary analysis in which only those with ≤2 cycles of conception attempts are included).

No restrictions on duration of periodontitis are included. Given that periodontitis is a chronic, ongoing condition, a trial excluding those with certain patterns of disease history (e.g. diagnosis greater than 4 years before conception attempt initiation) may limit the utility of the findings. We exclude participants who are currently undergoing treatment and therefore could not ethically be randomized to no treatment. We consider treatment within 12 months before trial entry as 'current treatment' and do not exclude potential participants with treatment more than 12 months before trial entry.

Emulation: Participants reporting a history of periodontitis diagnosis would be eligible for inclusion. As in the target trial, we

TABLE 2 Target and emulation trial protocol.

Component	Target trial specification	Target trial emulation
Eligibility criteria	• Identify as female, assigned female at birth, or have uterus • Aged 21–45 • Not using fertility treatment or contraception • Attempting pregnancy with a single partner • Not pregnant at enrolment • Resident of the United States or Canada • ≤6 months of pregnancy attempts at enrolment • Clinically confirmed periodontitis • Not currently undergoing treatment for periodontitis	• Same, except periodontitis is determined by a self-report of diagnosis and we lack data on whether participants are currently undergoing treatment for periodontitis
Treatment strategies	• Treatment: Participants received one of a few prespecified treatment regimens appropriate for different degrees of disease severity* • Control: no treatment before conception attempts	• Treatment is positive response to the question 'Have you ever had treatment for periodontitis?' within 12 months of initiating conception attempts • Control is negative response to above question.
Treatment assignments	• Participants randomly assigned • Unblinded	• Assume random assignment within levels of baseline covariates
Time zero assignment	• Time zero begins at randomization	• Begins with first reported cycle of conception attempt
Follow up period	• Follow up ends at pregnancy, 12 months of follow up without a pregnancy, withdrawal, initiation of fertility treatment • Should look separately at shorter durations: i.e., first 3 months, first 6 months, etc.	Same
Outcome	• Pregnancy • Cycles of attempts until pregnancy	Same
Causal contrasts of interest	• Intent-to-treat and per-protocol	Per-protocol

*Designing specific treatment comparators is beyond the scope of this paper. Researchers conducting a target trial should consider clinical best practices, the likely clinical condition of their target population, and available data on treatment in the data source.

restrict to those with ≤ 6 months of conception attempts at enrolment. Since we are not in fact assigning treatment, we do not exclude participants actively undergoing treatment from the emulated trial.

3.3.2 | Treatment strategies

Target trial: Our aim was to estimate the effect of receiving periodontitis treatment compared with no treatment proximal to the initiation of conception attempts among females attempting pregnancy with 6 or fewer months of conception attempts. Because we place few restrictions on disease history or status, beyond requiring clinical confirmation and no active treatment, we anticipate heterogeneity in our hypothetical target sample in terms of disease severity. As such, we would specify a few specific types of periodontitis treatment appropriate for different disease stages/severity. Precisely defining these treatment regimens is beyond the scope of this paper. In the target trial, treatment would occur shortly after randomization and we would specify the time frame within which treatments must be completed.

Emulation: Prior scientific research suggests that any treatment effect would last a maximum of 12 months.¹⁸⁻²¹ Therefore, we categorized participants as exposed if they reported any treatment at any time during the 12 months before time zero. Due to the nature of the data available, we determined the time since reported treatment based on the age at time of treatment; we considered participants to be unexposed if the reported age at treatment was more than one year younger than their age at baseline. Finally, while we intend to estimate the effects of treatment, it is important to be aware that the measured variable is self-report of treatment history. Measurement error in this variable may need to be considered in the analyses.

3.3.3 | Follow up period and 'time zero'

Target trial: 'Time zero' corresponds to the point of randomization. Patients are followed for a minimum of 12 months to reflect the fact that changes to systemic health after periodontitis treatment are believed to last for up to 6 months, with the potential for up to 12 months.¹⁸⁻²¹

Emulation: 'Time zero' is the initiation of conception attempts (even if this occurred before enrolment). Follow up continues for up to 12 months after cohort enrolment, until pregnancy, loss to follow-up or administrative censoring.

3.3.4 | Assignment procedures

Target trial: Randomize participants to receive either periodontal treatment (as previously defined) or no treatment.

Emulation: Random assignment will be emulated by adjusting for confounding factors related to treatment receipt and TTP: years between periodontitis diagnosis and enrolment, body mass index, parity, income, education, sugar-sweetened beverage consumption, smoking status, diabetes and self-rated oral health.

3.3.5 | Outcomes

Target trial: Time (in menstrual cycles) to pregnancy.

Emulation: Self-reported TTP, calculated from data obtained in enrolment and follow up questionnaires. Participant reports of TTP have previously been validated and >90% of participants had agreement within 1 day for their date of LMP reported on a questionnaire and an online fertility tracking app.¹⁰ Additional validity efforts, including cross-referencing self-reported LMP with data collected from a fertility app, may be warranted to improve validity.

3.3.6 | Causal contrast of interest

Target trial: The causal contrast of interest refers to the comparison that will be estimated from the target trial. The intention-to-treat comparison or 'as randomized' comparison, is generally regarded as the preferred approach to analysing trial data, because it enables the analyst to retain the primary benefit of randomization: confounding reduction.²² However, the intention-to-treat contrast describes the effect of randomization to the treatment strategies of interest and can be less informative when there is non-adherence. Another causal contrast of interest in a randomized trial is the 'per-protocol effect' which describes the effect of actually receiving assigned treatment.

In this application, the target trial would estimate the intention-to-treat and per-protocol effect.

Emulation: In the emulation, we are interested in the effect of receiving treatment, so we emulate the per-protocol effect. We use self-reported treatment receipt as a proxy for actual treatment receipt.

3.3.7 | Analysis plan

Target trial: To estimate the intention-to-treat effect, TTP among those randomized to receive treatment is compared with those who were randomized not to receive treatment. The per-protocol effect requires adjustment for baseline and post-baseline factors related to whether or not participants adhered to their assigned treatment strategy.¹ We would use proportional probabilities regression models, an analog to the Cox proportional hazards model that models discrete probabilities rather than a smooth hazard function, to estimate fecundability ratios and 95% confidence intervals comparing those who received treatment to those who did not.²³ In a trial with follow-up data, we may need to adjust for post-baseline factors if they are related to loss to follow up,²² to mitigate the potential for selection bias.²⁴

Emulation: TTP would be compared between those with and without a history of treatment for periodontitis, adjusting for baseline confounders. The statistical analyses would be the same. We could also consider adjusting for post-baseline factors related to loss to follow up.

3.3.8 | Interpreting the emulation

After finalizing the target trial and emulation protocol, it is useful to revisit the specified causal question. This is because analytic decisions made while designing the emulation can influence the question that can be answered. Our original research question was 'Among females with periodontitis during the preconception period, how does receiving treatment for periodontitis affect TTP?' After specifying the target trial, we had identified a more specific causal question: 'Among females with diagnosed periodontitis who self-identify as pregnancy planners and have been attempting conception for no more than 6 cycles *at the time of enrolment into the study*, would their TTP, *counted from initiation of conception attempts*, have been different if they were

assigned to treatment appropriate for their disease severity in the preconception period compared to if they were not assigned to treatment during the preconception period?'. In considering the possible options for emulation with the PRESTO data, we further refined our causal question to ask 'Among females with diagnosed periodontitis who self-identify as pregnancy planners and have been attempting conception for no more than 6 cycles at the time of enrolment into the study, would their TTP, counted from initiation of conception attempts for a maximum of 12 months, have been different if they were assigned to *and received treatment* appropriate for their disease severity in the preconception period no more than 12 months before study entry compared to if they were not assigned to *and did not receive* treatment during this time? The iterative process through which our target trial specification influenced our causal question is detailed in [Figure 3](#). The interpretation would be limited by the fact that we rely on self-report to assess both diagnosis and treatment. The resulting misclassification would have the potential to bias any observed associations. The use of quantitative bias analysis could provide insights into the potential influence of this bias, to aid in interpretation.^{25,26}

Initial research question: Among females with periodontitis during the preconception period, how does receiving treatment for periodontitis affect TTP?

Reformulating as a causal question: Among females with diagnosed periodontitis, would their TTP have been different if they were assigned to treatment in the preconception period compared to if they had not assigned to treatment during the preconception period?

Incorporating treatment type details: Among females with diagnosed periodontitis, would their TTP have been different if they were assigned to treatment appropriate for their disease severity in the preconception period compared to if they were not assigned to treatment during the preconception period?

Defining the population of interest: Among females with diagnosed periodontitis who self-identify as pregnancy planners and have been attempting conception for no more than 6 cycles, would their TTP have been different if they were assigned to treatment appropriate for their disease severity in the preconception period compared to if they were not assigned to treatment during the preconception period?

Defining time zero: Among females with diagnosed periodontitis who self-identify as pregnancy planners and have been attempting conception for no more than 6 cycles at the time of enrollment into the study, would their TTP, counted from initiation of conception attempts, have been different if they were assigned to treatment appropriate for their disease severity in the preconception period compared to if they were not assigned to treatment during the preconception period?

Defining treatment strategies: Among females with diagnosed periodontitis who self-identify as pregnancy planners and have been attempting conception for no more than 6 cycles at the time of enrollment into the study, would their TTP, counted from initiation of conception attempts, have been different if they were assigned to treatment appropriate for their disease severity in the preconception period no more than 12 months before study entry compared to if they were not assigned to treatment during this time?

Specifying follow-up duration: Among females with diagnosed periodontitis who self-identify as pregnancy planners and have been attempting conception for no more than 6 cycles at the time of enrollment into the study, would their TTP, counted from initiation of conception attempts for a maximum of 12 months, have been different if they were assigned to treatment appropriate for their disease severity in the preconception period no more than 12 months before study entry compared to if they were not assigned to treatment during this time?

Clarifying the causal contrast (per-protocol effect): Among females with diagnosed periodontitis who self-identify as pregnancy planners and have been attempting conception for no more than 6 cycles at the time of enrollment into the study, would their TTP, counted from initiation of conception attempts for a maximum of 12 months, have been different if they were assigned to and received treatment appropriate for their disease severity in the preconception period no more than 12 months before study entry compared to if they were not assigned to and did not receive treatment during this time?

FIGURE 3 Iterative process of specifying a causal question for the effect of preconception periodontitis treatment on time to pregnancy.

3.3.9 | Barriers to implementation of the proposed emulation in the PRESTO data

Here, we report only the target trial and emulation plans, due to barriers to implementation we identified through this process. Most importantly, our data lack sufficient detail about treatments received, including type and date, to enable a detailed specification of comparators. This required an alteration to our causal question which could affect interpretability of results. We also lack details about the criteria used by individual dental care providers to diagnose periodontitis, as well as disease severity beyond disease duration, which may limit our ability to successfully emulate randomization as disease severity is an important potential confounder. These two barriers could be resolved through collection of more detailed data. Though the target trial framework can improve causal inference from observational data, it is not a panacea and the data quality should be considered when contemplating the potential for inference from a target trial emulation.

4 | DISCUSSION

We detail the specification of a target trial and observational emulation protocol to evaluate the potential effect of preconception periodontitis treatment on TTP. In the process of specifying the target trial, we identified important limitations in our available data source. Because the target trial framework has the potential to aid in the creation of valid and clinically relevant observational oral health research, we share these challenges to aid in the collection of future data for trial emulations.

We gained several insights related to the potential for trial emulation in oral health research. Data quality is critical. The target trial framework originated in claims databases, which have large study sizes and considerable treatment details.¹ However, the use of claims data for oral health research is nascent and many large claims databases lack information on dental claims and/or are limited to procedural codes. An effective target trial involves precise specification of detailed treatment comparators. Validated self-report questions related to periodontitis treatment do not routinely collect much detail about treatment,^{11,12} which may limit their utility in target trial emulations. Self-reported data are additionally limited by the lack of clinical assessments of periodontal health. As such, researchers should consider how they would define periodontitis in the inclusion criteria for a trial. For example, if chronic inflammation is most etiologically important, then the eligibility criteria for a target trial may reference attachment loss and questions related to disease history would be important for an emulation. If current, active inflammation is more important, then questions related to current oral health would be most informative. However, this does not effectively address the fact that there can be considerable heterogeneity in how individual dental care providers diagnose periodontitis, which means that a history of diagnosis may have widely variable clinical implications depending on the case definition employed by the provider.²⁷ The

development of novel and carefully validated self-reported measures capturing disease and treatment details could facilitate future target trial emulations. Applying the target trial emulation protocol to specific research questions can be an invaluable tool to identify limitations in currently available measures and data and help inform future research directions.

Specifying a trial emulation protocol also revealed the complexity of managing multiple events of interest. Our cohort varied in terms of when participants received treatment, initiated conception attempts and enrolled in the study. In designing our emulation, we had to consider the potential for bias depending on how we designated 'time zero.' Oral health researchers using the target trial framework should dedicate time to understanding the interplay between the timing of treatment receipt and entry into an observational study to reduce the chances of bias. Conducting the emulation is further complicated by unknowns around the potential duration of the benefit of periodontitis treatment on systemic outcomes. There seems to be consensus that reductions in circulating inflammatory markers after periodontitis treatment persist for 3–6 months, and potentially up to 12.^{18–21} Defining an appropriate duration of follow-up can be challenging when there is uncertainty around the expected duration of treatment benefit.

By detailing our target trial specification and emulation protocol, we aimed to provide recommendations and guidance to facilitate the use of the target trial framework in oral health epidemiology. Though we did not conduct the trial emulation, our specified trial could serve as a blueprint for future trial emulations. We hope that our insights can help researchers plan and conduct effective target trial emulations for the purposes of evaluating research questions in oral health.

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DATA AVAILABILITY STATEMENT

Participants did not provide informed consent to share their data, thus individual-level data are not publicly available.

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REFERENCES

1. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183(8):758–764.
2. Daalderop LA, Wieland BV, Tomsin K, et al. Periodontal disease and pregnancy outcomes: overview of systematic reviews. *JDR Clinical & Translational Research*. 2018;3(1):10–27.

3. Iheozor-Ejiofor Z, Middleton P, Esposito M, Glenny AM. Treating periodontal disease for preventing adverse birth outcomes in pregnant women. *Cochrane Database of Systematic Reviews [Internet]*. 2017;6(6):CD005297.
4. Goldenberg RL, Culhane JF. Preterm birth and periodontal disease. *N Engl J Med*. 2006;355(18):1925-1927.
5. Xiong X, Buekens P, Goldenberg RL, Offenbacher S, Qian X. Optimal timing of periodontal disease treatment for prevention of adverse pregnancy outcomes: before or during pregnancy? *Am J Obstet Gynecol*. 2011;205(2):111.e1-111.e6.
6. Bond JC, Wise LA, Willis SK, et al. Self-reported periodontitis and fecundability in a population of pregnancy planners. *Hum Reprod*. 2021;36(8):2298-2308.
7. Bond JC, Wise LA, Fox MP, et al. Preconception periodontitis and risk of spontaneous abortion in a prospective cohort study. *Am J Epidemiol*. 2023;192:1509-1521. doi:10.1093/aje/kwad142
8. Lawrie TA, Betrán AP, Singata-Madliki M, et al. Participant recruitment and retention in longitudinal preconception randomized trials: lessons learnt from the calcium and pre-eclampsia (CAP) trial. *Trials*. 2017;18(1):500.
9. Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. *J Clin Epidemiol*. 2016;1(79):70-75.
10. Wise LA, Rothman KJ, Mikkelsen EM, et al. Design and conduct of an internet-based preconception cohort study in North America: pregnancy study online (PRESTO). *Paediatr Perinat Epidemiol*. 2015;29(4):360-371.
11. Eke PI, Dye B. Assessment of self-report measures for predicting population prevalence of periodontitis. *J Periodontol*. 2009;80(9):1371-1379.
12. Eke PI, Dye BA, Wei L, et al. Self-reported measures for surveillance of periodontitis. *J Dent Res*. 2013;92(11):1041-1047.
13. Heaton B, Gordon NB, Garcia RI, et al. A clinical validation of self-reported periodontitis among participants in the Black Women's Health Study. *J Periodontol*. 2017;88(6):582-592. <https://doi.org/10.1902/jop.2017.160678>
14. Goetghebuer E, le Cessie S, De Stavola B, Moodie EE, Waernbaum I. Initiative 'on behalf of' the topic group causal inference (TG7) of the STRATOS. Formulating causal questions and principled statistical answers. *Stat Med*. 2020;39(30):4922-4948.
15. Hernan MA, Robins JM. *Causal Inference: What if [Internet]*. Chapman & Hall/CRC; 2020 <https://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/>
16. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Chronic Dis*. 1967;20:637-648.
17. Kwon T, Lamster IB, Levin L. Current concepts in the Management of Periodontitis. *Int Dent J*. 2021;71(6):462-476.
18. Rose-Hill S, Ford P, Leishman S, et al. Improved periodontal health and cardiovascular risk. *Aust Dent J*. 2011;56(4):352-357.
19. López NJ, Quintero A, Casanova PA, Ibieta CI, Baelum V, López R. Effects of periodontal therapy on systemic markers of inflammation in patients with metabolic syndrome: a controlled clinical trial. *J Periodontol*. 2012;83(3):267-278.
20. D'Aiuto F, Gkraniats N, Bhowruth D, et al. Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. *The Lancet Diabetes & Endocrinology*. 2018;6(12):954-965.
21. D'Isidoro O, Perrotti V, Hui WL, Piattelli A, Iaculli F, Quarant A. The impact of non-surgical therapy of periodontal disease on surrogate markers for cardiovascular disease: a literature review. *Am J Dent*. 2019;32(4), 191-200.
22. Hernan MA, Hernandez-Diaz S. Beyond the intention-to-treat in comparative effectiveness research. *Clin Trials*. 2011;9(1):48-55.
23. Weinberg CR, Wilcox AJ, Baird DD. Reduced fecundability in women with prenatal exposure to cigarette smoking. *Am J Epidemiol*. 1989;129(5):1072-1078.
24. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology*. 2004;15(5):615-625.
25. Bond JC, Fox MP, Wise LA, Heaton B. Quantitative assessment of systematic bias: a guide for researchers. *J Dent Res*. 2023;102(2):1288-1291.
26. Fox MP, MacLehose RF, Lash TL. *Applying Quantitative Bias Analysis to Epidemiologic Data*. 2nd ed. Springer Nature Switzerland AG; 2021.
27. Ke L, Nogueira G, Thomson WM. Influence of case definitions on epidemiological estimates of periodontitis prevalence and its associations with smoking and OHRQoL. *Community Dent Oral Epidemiol*. 2023;51(2):194-200.

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