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COMMENTARY

Preference-based controlled design: toward increased patients' engagement, efficiency, and external validity of cardiovascular clinical trials

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Abstract

Randomized controlled trials (RCTs) are the gold standard for evaluating clinical interventions, but their limitations—particularly in settings where strong patient preferences exist—can impair recruitment, compliance, and external validity. In cardiovascular research, these challenges are pronounced in trials comparing treatments that differ substantially in invasiveness, burden, or delivery mode. We describe how patient preference-controlled designs can enhance trial efficiency and generalizability by engaging patients as active participants in the allocation process. Although nonrandom allocation introduces potential for confounding, we argue that these trials can produce valid and robust treatment effect estimates when key confounding influences—such as physician bias, functional status, and health beliefs—are prospectively measured and controlled. Preference, under appropriate design conditions, may function as a valid instrumental variable. Furthermore, we introduce a hybrid trial design that incorporates both randomized and preference-based cohorts. This approach allows for separate and combined effect estimates, preserving the internal validity of randomization while expanding recruitment and improving external validity. Bayesian modeling frameworks can be used to integrate treatment effect estimates across cohorts while adjusting for differences in preference strength and confounding structure. In summary, patient preference-controlled trials represent a rigorous, underutilized methodology in cardiovascular research. By prospectively addressing and quantifying bias, they offer a practical solution to the limitations of both traditional RCTs and retrospective observational studies. We advocate for the development of formal design and reporting guidelines and encourage their consideration in trials where patient empowerment and generalizability are critical.

Keywords: External validity; Measured and unmeasured confounding; Patient preference trial; Prospective nonrandomized trial; Randomized trial; Prospective bias mitigation

Randomization minimizes biases and balances known and unknown confounders across treatment groups and is the gold standard allocation method for clinical trials evaluating health-care interventions [1]. However, randomization disregards patient preferences, which can result in reluctance to participate or poor compliance with assigned treatments. In fact, randomized trials often recruit a smaller and more selective subset of the intended target population, limiting generalizability and statistical power, and substantial levels of noncompliance with treatment allocation among enrolled participants introduce postrandomization bias [2–4]. Contemporary systematic reviews report that ~25% of initiated randomized controlled trials (RCTs) are discontinued, with poor recruitment the leading cause, and that many trials fail to reach their original sample size or require extensions [5,6]. A principal driver of poor recruitment is patients declining randomization [2–4].

Nonrandomized allocation methods, either as standalone approaches or in combination with randomization, offer a potential means to address these challenges and mitigate their impact on trial outcomes and external validity. Despite their

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What is new?

- Patient preference-controlled trials offer a pragmatic alternative or complement to randomization, addressing limitations in representativeness, compliance, and external validity in cardiovascular research.
- This design actively involves patients in treatment allocation while prospectively mitigating bias, allowing for more meaningful engagement and improved trial efficiency.
- The article proposes a structured framework for minimizing confounding and validating patient preference as a quasirandom instrument under specific design conditions.
- Hybrid trial designs, combining randomized and preference-controlled cohorts, can enhance statistical power and generalizability while expanding recruitment.
- Incorporating patient preference into trial design should be considered in settings where randomization may limit participation or introduce systematic bias, especially when treatments differ substantially in burden or invasiveness.

potential advantages, prospective nonrandom allocation methods remain underutilized in cardiovascular research [7]. Instead, most nonrandomized comparative effectiveness studies rely on retrospective observational datasets, which lack detailed information about the rationale behind treatment allocation and key confounders [7,8]. This gap between RCTs and retrospective observational studies highlights the need for innovative designs using prospective controlled allocation methods. Herein, we propose that although randomized trials should remain the preferred approach whenever feasible, a prospectively controlled patient-preference trial represents a practical alternative—or complement—when randomization is infeasible or when high rates of refusal threaten enrollment, adherence, or generalizability.

1. Patient preference trials can transform patients from passive to active trial participants

Engaging patients in clinical research is essential to inform patient-centered care. When patients are involved in trial design, studies better align with real-world needs and patient perspectives, which often differ from those of physicians [9]. This enhances the relevance of findings and facilitates their translation into clinical settings. Although patient representatives are increasingly engaged in decisions related to study design, the role of the patients who participate in cardiovascular trials has not evolved significantly and remains largely passive. We propose advancing the concept of patient engagement in cardiovascular trials by incorporating individual patient preferences into the trial design—through patient preference–controlled trials. This approach addresses reluctance toward randomization and improves trial representativeness and efficiency by increasing participation and compliance.

Although patient preference trials have been conducted in psychology and a few other medical specialties, the concept has not gained widespread recognition among cardiovascular trialists [10]. Building on framework of the trials, we describe how patient preference–controlled trials, in which bias is minimized by prospectively avoiding and quantifying confounding influences on patient preferences, could empower patients while improving trial efficiency and external validity of cardiovascular trials.

2. The patient preference–controlled trial

In this approach, eligible and prospectively enrolled patients select their preferred treatment, but potential influences on this choice—such as physician recommendations, external biases, patient characteristics or subjective beliefs—are minimized as part of the trial protocol, allowing reliable estimates of treatment effects.

Like randomization, patient preference can be seen as a very strong instrumental variable (IV) [11], provided that the trial is carefully designed to satisfy the core conditions required for a valid IV instrument (see Figure and legend). The independence criterion (no confounding) poses a critical challenge for patient preference–controlled trials and requires careful consideration, but can be more plausibly met if the trial is carefully designed to prospectively measure and adjust for key confounders that influence both patient preference and outcome, and analytical methods account for residual confounding (eg, through sensitivity analyses, principal stratification, or control function approaches). Patient preference may violate the exclusion restriction criterion, as it can reflect unmeasured factors—such as health beliefs, motivation, or functional status—that independently influence outcomes. To address this concern, the trial needs to prospectively collect relevant covariates and conduct sensitivity analyses to assess the robustness of the findings to potential violations. We propose that patient preference-controlled allocation be considered a nonrandomized alternative or complement to randomization.

3. Mitigating bias prospectively

It is critical that in patient preference–controlled trials, the factors that influence patient treatment choices [12] are carefully identified and measured. This includes not only

Table. 1 Potential confounders[a] of the relationship between patient preference and the risk of the primary outcome

Variable type	Comment	Examples of variables
Clinical status	Drives preference for faster/less invasive options; predicts events	New York Heart Association class, Quality of life scores
Functional capacity	Worse function may result in preference for less invasive therapy, and correlates with prognosis	6-min walk, gait speed
Frailty	Frail patients favor less invasive care	Frailty scores
Comorbidities	Higher burden may result in preference for lower burden care	Charlson comorbidity index, Elixhauser comorbidity measures
Prior procedures	Experience shapes preferences and correlates with prognosis	Prior surgery, prior percutaneous interventions
Risk tolerance	Affects willingness for invasive or experimental therapies, associated with adherence/rehab	Domain-specific-risk taking (DOSPERT) scale
Health literacy	May affect propensity to defer decisions to clinician and correlate with outcomes	Brief Health Literacy Screen; Short Test of Functional Health Literacy in Adults
Cognitive status	Impacts decision-making capacity and follow-through	Mini-Cog; Montreal Cognitive Assessment
Mental health	Anxiety/depression influence preferences, recovery, and patient-reported outcomes	Hospital Anxiety and Depression Scale; Patient Health Questionnaire-4
Social support	Low support may steer toward shorter recovery options; predicts readmission	ENRICHD Social Support Instrument
Caregiver burden	Availability/strain influences treatment choice and adherence	Zarit Burden Interview; presence of primary caregiver
Work/role	Time constraints and role demands steer preferences	Employment status; anticipated days off work; caregiving responsibilities
Distance and logistics	Access barriers bias choices; affect follow-up and outcomes	Estimated travel time; number of required visits; need for transport
Economic pressure	Costs/time away from work bias choices; socioeconomic status predicts outcomes	Household income/education bands; out-of-pocket cost concern (Likert scale)
Information exposure	External sources shape preferences and correlate with behaviors	Number/type of sources (clinician, internet, social media, peers/family); ''most influential source'' item
Trust and clinician influence	Strong recommendations can steer choice and correlate with case severity	Strength of clinician recommendation (0–10 scale); Wake Forest Physician Trust Scale
Adherence propensity	Past adherence predicts outcomes and may shape preference	Morisky Medication Adherence Scale (8-item)
Preference strength	Core driver of allocation; also predicts engagement/outcomes	Preference strength (0–10 scale); willingness to be randomized (yes/no)

[a] Confounders of the relationship between patient preference and risk of an outcome are expected to be context specific and should be assessed for each specific trial setting.

traditional demographic, socioeconomic, and clinical variables but also aspects of the clinical interaction, such as biases—intentional or unintentional—introduced by health-care providers (Table 1).

Physicians and staff may unknowingly guide patients toward one treatment over another through recommendations or subtle cues, introducing confounding that can be challenging to fully control for after the fact if they have not been addressed as part of the trial protocol [13]. It is essential to create a neutral decision-making environment by selecting a target population where genuine equipoise between treatment options exists. Standardizing how information is presented to patients, such as through unbiased educational materials and ''neutral'' clinicians who do not favor either treatment, can help reduce the impact of provider biases. In addition, prospectively capturing clinicians' treatment preferences—and the strength of their recommendations—allows adjustment for residual confounding.

Beyond the health-care setting, patients are also influenced by external factors such as online resources, social media, and input from family or friends. Exposure and interpretation of these influences could be associated with patient factors that also affect the risk of adverse clinical outcomes [14].

Avoiding confounding is easier when the study interventions are less readily distinguishable for patients, such as two different coronary stents or two drugs with similar routes of administration and side effects. In this setting, patients are unlikely to have a strong preference for either the treatment arm and the risk of bias with a patient preference–controlled approach is expected to be low as long as external influences on the patient's choice from the study team or other sources are minimized.

Avoiding confounding becomes more challenging when the interventions being compared are easily distinguishable to patients and their families or have very different mechanisms and invasiveness (eg, when comparing surgery with transcatheter interventions or medical therapy). Although patient preference–controlled trials are more challenging in these situations, it is when patients have stronger preferences that they are more reluctant to be allocated to a treatment ''by chance'' and when this trial design may be more effective.

In fact, in randomized trials comparing surgical to transcatheter procedures, crossover and deviations from the randomized assignment as well as loss to follow-up have been shown to disproportionate in patients randomized to the surgical vs. transcatheter treatment arms and this may significantly affect the internal validity of these trials [15]. If the factors influencing patient preference in these studies can be adequately controlled for, a patient preference–controlled approach may be particularly effective at facilitating participation and reducing feelings of

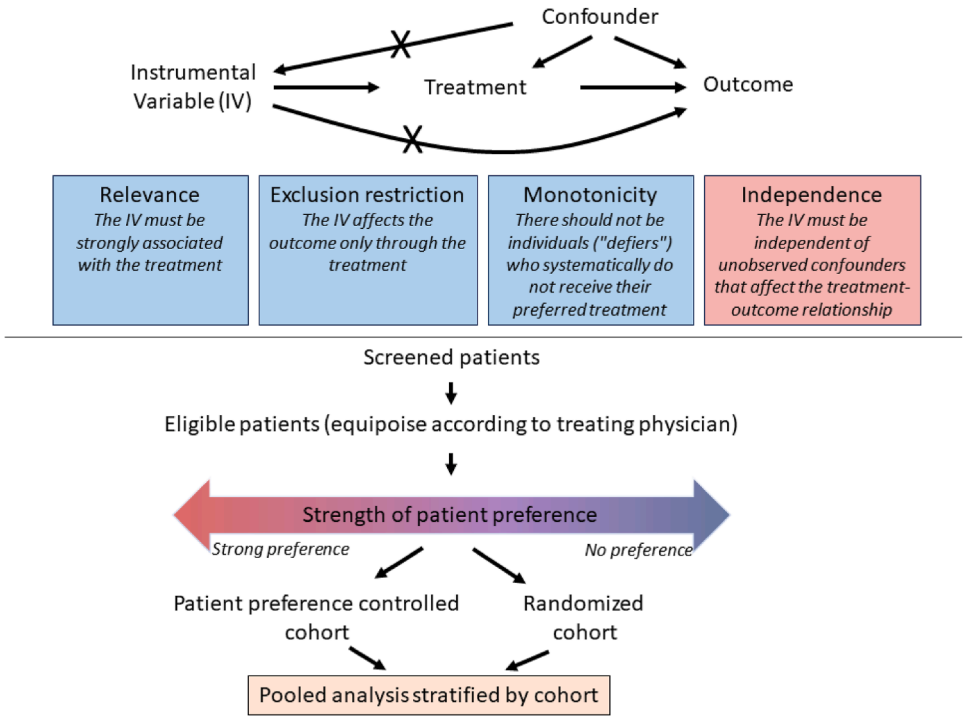

Figure. The patient preference–controlled trial can be a strong instrument and can complement the randomized trial. Upper panel: An instrument is a variable that helps isolate the causal effect of the treatment (exposure) on the outcome. To be valid, the instrument must satisfy the four core criteria. (1) Relevance: The instrument must be strongly associated with the treatment or exposure. In a well-designed patient preference trial, in which the patient choses his or her treatment, he or she would be expected to receive that treatment. (2) Exclusion restriction: The instrument should affect the outcome only through its effect on the treatment and not through any other pathway. Patient preference per se does not directly cause any outcome. (3) Independence (no confounding): The instrument must be independent of unmeasured confounders that influence both the treatment and the outcome. The independence criterion is the most challenging criterion for a patient preference–controlled trial, because there are many possible confounders that could affect both the patient preference and the risk of the outcome. (4) Monotonicity: There should be no ''defiers,'' meaning no individuals who systematically act against the direction of the instrument's influence on treatment. We would not expect any systematic discrepancy between the patients preferred treatment and the treatment he or she receives. When these criteria are met, IV analysis provides an unbiased estimate of the causal effect, even in the presence of unmeasured confounding between the exposure and outcome. Lower panel: Illustration of a hybrid trial design that stratifies patients into randomized and patient preference–controlled cohorts based on the strength of their treatment preferences. Eligible patients, determined to be in equipoise according to the treating physician, are assessed for their preference strength. Patients with little to no preference are enrolled in the randomized cohort, whereas those with moderate to strong preferences are directed to the patient preference–controlled cohort, where they receive their preferred treatment. This approach facilitates the inclusion of a broader patient population, improving trial efficiency, representativeness, and statistical power while addressing potential barriers to participation associated with randomization. The strength of patient preference can be measured systematically, and the threshold for assigning patients to the randomized vs. preference-controlled cohort can be adjusted based on the specific trial design. Alternatively, the preference-controlled cohort can be limited to patients who explicitly decline randomization.

disempowerment associated with randomization while also increasing trial efficiency and mitigating the risks of unequal protocol deviations and differential loss to follow-up.

4. A hybrid trial design integrating patient preference–controlled cohorts and randomized cohorts to increase representativeness and efficiency

A patient preference–controlled approach can also complement randomization within the same trial, increasing efficiency and external validity (Figure) [16].

Patients with minimal or no strong preference, who are willing to be randomized, can be enrolled in the randomized cohort. Those with moderate to strong preferences—who may refuse randomization or not be compliant with the randomized allocation—can be included in the patient preference-controlled cohort.

The randomized cohort and the patient preference-controlled cohort can be analyzed as separate strata into a unified trial framework. The hybrid designs allow for separate estimation of treatment effects within the two cohorts, while enabling a combined estimate to substantially improve the statistical power of the study. By including participants who would otherwise be excluded due to moderate to strong preferences, this approach enhances trial generalizability and boosts the effective sample size.

For instance, a Bayesian modeling framework provides a flexible structure for combining treatment effects across cohorts [17]. Prior distributions can be specified to define the relative contribution of each cohort to the overall treatment effect estimate. These priors can be updated based on the observed concordance between the two cohorts' treatment effects [18]. When the treatment effects align closely, the preference-controlled cohort can be weighted more heavily; when discrepancies arise, the model downweights its influence—thus preserving the integrity of the randomized evidence while still leveraging the broader patient population. Concretely, this can be performed by placing weakly informative priors on each cohort-specific treatment effect and using a hierarchical borrowing prior that shrinks the preference cohort toward the randomized cohort when consistent (eg, a commensurate/hierarchical specification with a data-driven similarity parameter assigned a half-Cauchy or inverse-gamma prior) [17].

This integrated approach provides a more comprehensive framework for evaluating health-care interventions, producing results that are both scientifically rigorous and practically meaningful for diverse patient populations and mitigating the risks associated with nocebo effects, treatment noncompliance, and crossover [16].

5. When to consider a preference trial

A stand-alone preference trial may be most useful when very high refusal of randomization is expected, such that an RCT would be underenrolled, selective or prone to crossover to the point of being unfeasible. Typical contexts include comparisons of distinctly different treatments, such as invasive procedures vs. medical therapy, where the invasive option entails greater upfront risk but potential long-term benefit. As an example, the ISCHEMIA trial, which randomized patients with stable coronary artery disease to an initial invasive or conservative strategy, was forced to reduce its target enrollment by nearly half owing to slow recruitment and reluctance to accept random allocation [3,19]. In such settings, allowing patients to choose within a bias-mitigated, prospectively measured framework can enhance feasibility, participation, and representativeness, while yielding considerably more credible estimates of effectiveness than a conventional observational design. However, even in such settings a hybrid partially randomized patient preference design may be more suitable if a meaningful subset is willing to accept randomization.

A hybrid design can be considered more broadly. It can increase participation and improve external validity when *strong preferences* are likely to drive high refusal (eg, *invasive vs less-invasive revascularization strategies*), and it is also reasonable in *unblinded trials* where explicit preferences may be modest but *random allocation itself deters participation*—thereby preserving randomized internal validity while extending applicability to patients unlikely to accept randomization [2]. In fact, a prespecified preference cohort may be considered as a complement to most RCTs, particularly when substantial refusal is anticipated, as often observed among underrepresented groups such as women and minority patients [20].

It should be noted that recruiting a preference cohort in parallel to the RCT cohort increases the number of patients and infers costs. In trials where randomization is well accepted and recruitment proceeds as planned, it may be reasonable to omit the preference cohort, as the incremental scientific value would be small. However, when trial procedures, follow-up schedules, and data capture are harmonized, the incremental burden per patient is modest—largely limited to recording variables related to preference strength at enrollment—while the benefits can be substantial: improved recruitment/retention and inclusion of patients who would otherwise decline participation, and more generalizable effect estimates. Empirical experience from partially randomized patient preference studies in other fields supports the feasibility of this hybrid approach [21].

6. Challenges and future directions

We have clarified that patient preference as allocation method can only be expected to yield unbiased estimates of treatment effect if confounding can be adequately controlled. Although, technically, only factors that influence both the patient's preferred treatment and the outcome

need to be controlled for (Figure), it can be difficult to determine with certainty which influences affect the outcome (Table). Understanding how patient preferences are formed and what factors drives them requires dedicated research; traditional randomized trials offer the ideal platform for qualitative as well as quantitative analysis on patients who refuse to participate due to personal preferences. This approach can generate important data to support robust statistical control in patient preference−controlled trials. Directed acyclic graphs that include all conceivable confounders can also be used during trial design to ensure that all potential confounders are controlled for [22].

Another key practical limitation is the challenge in assessing the effectiveness of bias control. Without transparent and comprehensive reporting on the procedures used to mitigate bias, it is difficult for readers, journal editors or regulatory bodies to judge the quality of control achieved. Accurate assessment of bias risk in these trials requires not only clear and detailed study protocols, case report forms, and analytical plans, but also detailed disclosure of any protocol deviations or lapses in adherence to planned methods.

If patient preference is to be used as allocation method in clinical trials, guidelines for its use are warranted. We believe such guidelines should include prospective identification of confounders that could potentially influence patient preference and clear a priori specification of how these confounders will be controlled. Reporting of results from these trials should also include sufficient information on the procedures used to control for confounding and any breeches in these processes.

7. Conclusion

In conclusion, using patient preference as a prospective allocation method may serve as an alternative or a complement to randomization in comparative effectiveness clinical trials, especially when randomization may lead to patient disempowerment or low external validity. By prospectively mitigating and quantifying expected sources of bias, patient preference−controlled trials may overcome many of the limitations of traditional nonrandomized comparative effectiveness studies.

CRediT authorship contribution statement

Bjorn Redfors: Writing − review & editing, Writing − original draft, Visualization, Project administration, Methodology, Conceptualization. **Sigrid Sandner:** Writing − review & editing, Methodology. **Judy Zhong:** Writing − review & editing, Methodology. **Mario Gaudino:** Writing − review & editing, Writing − original draft, Methodology, Conceptualization.

Declaration of competing interest

There are no competing interests for any authors.

Data availability

No data was used for the research described in the article.

References

[1] Pirondini L, Gregson J, Owen R, Collier T, Pocock S. Covariate adjustment in cardiovascular randomized controlled trials: its value, current practice, and need for improvement. JACC Heart Fail 2022; 10:297−305.
[2] Gaudino M, Kappetein AP, Di Franco A, Bagiella E, Bhatt DL, Boening A, et al. Randomized trials in cardiac surgery: JACC review topic of the week. J Am Coll Cardiol 2020;75:1593−604.
[3] Rodriguez F, Hochman JS, Xu Y, Reynolds HR, Berger JS, Mavromichalis S, et al. Screening for participants in the ISCHEMIA trial: implications for clinical research. J Clin Transl Sci 2022;6:e90.
[4] O'Neill ZR, Deptuck HM, Quong L, Maclean G, Villaluna K, King-Azote P, et al. Who says ''no'' to participating in stroke clinical trials and why: an observational study from the Vancouver stroke program. Trials 2019;20:313.
[5] Kasenda B, von Elm E, You J, Blümle A, Tomonaga Y, Saccilotto R, et al. Prevalence, characteristics, and publication of discontinued randomized trials. Jama 2014;311:1045−51.
[6] McDonald AM, Knight RC, Campbell MK, Entwistle VA, Grant AM, Cook JA, et al. What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies. Trials 2006;7:9.
[7] Redfors B. Improving registry-based observational comparative effectiveness studies by prospectively incorporating robust treatment preference instruments. JACC Adv 2023;2:100413.
[8] Vandenbroucke JP. When are observational studies as credible as randomised trials? Lancet 2004;363:1728−31.
[9] Stolker JM, Spertus JA, Cohen DJ, Jones PG, Jain KK, Bamberger E, et al. Rethinking composite end points in clinical trials: insights from patients and trialists. Circulation 2014;130:1254−61.
[10] Bradley-Gibride J, Bradley C. Partially randomized preference trial design. In: Encyclopedia of Research DesignVol.2. Thousand Oaks: Sage; 2010:1009−15.
[11] Angrist JD, Imbens GW, Rubin DB. Identification of causal effects using instrumental variables. J Am Stat Assoc 1996;91:444−55.
[12] Rubin DB. Causal inference using potential outcomes: design, modeling, decisions. J Am Stat Assoc 2005;100:322−31.
[13] Tversky A, Kahneman D. The framing of decisions and the psychology of choice. Science (New York, NY) 1981;211:453−8.
[14] Tan SS, Goonawardene N. Internet health information seeking and the patient-physician relationship: a systematic review. J Med Internet Res 2017;19:e9.
[15] Barili F, Brophy JM, Ronco D, Myers PO, Uva MS, Almeida RMS, et al. Risk of bias in randomized clinical trials comparing transcatheter and surgical aortic valve replacement: a systematic review and meta-analysis. JAMA Netw open 2023;6:e2249321.
[16] Patients' preferences within randomised trials: systematic review and patient level meta-analysis. BMJ 2008;337:a1864.

[17] Hobbs BP, Sargent DJ, Carlin BP. Commensurate priors for incorporating historical information in clinical trials using general and generalized linear models. Bayesian Anal 2012;7:639−74.
[18] Ibrahim JG, Chen MH, Gwon Y, Chen F. The power prior: theory and applications. Stat Med 2015;34:3724−49.
[19] Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, et al. Initial invasive or conservative strategy for stable coronary disease. N Engl J Med 2020;382:1395−407.
[20] Redfors B, Spertus JA, Yancy C, Masterson-Creber R, Stone GW, Gaudino MFL. Expanding revascularization trials to women and underserved minorities and shifting to patient-centered outcomes: RECHARGE trials program. Curr Opin Cardiol 2024;39:478−84.
[21] Wasmann KA, Wijsman P, van Dieren S, Bemelman W, Buskens C. Partially randomised patient preference trials as an alternative design to randomised controlled trials: systematic review and meta-analyses. BMJ Open 2019;9:e031151.
[22] Hernán MA, Wang W, Leaf DE. Target trial emulation: a framework for causal inference from observational data. JAMA 2022;328:2446−7.