A novel approach to assess dynamic treatment regimes embedded in a SMART with an ordinal outcome

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Sequential multiple assignment randomized trials (SMARTs) are used to construct data-driven optimal intervention strategies for subjects based on their intervention and covariate histories in different branches of health and behavioral sciences where a sequence of interventions is given to a participant. Sequential intervention strategies are often called dynamic treatment regimes (DTR). In the existing literature, the majority of the analysis methodologies for SMART data assume a continuous primary outcome. However, ordinal outcomes are also quite common in clinical practice. In this work, first, we introduce the notion of generalized odds ratio (GOR) to compare two DTRs embedded in a SMART with an ordinal outcome and discuss some combinatorial properties of this measure. Next, we propose a likelihood-based approach to estimate GOR from SMART data, and derive the asymptotic properties of its estimate. We discuss alternative ways to estimate GOR using concordant-discordant pairs and two-sample \(U\)-statistic. We derive the required sample size formula for designing SMARTs with ordinal outcomes based on GOR. A simulation study shows the performance of the estimated GOR in terms of the estimated power corresponding to the derived sample size. The methodology is applied to analyze data from the SMART+ study, conducted in the UK, to improve carbohydrate periodization behavior in athletes using a menu planner mobile application, Hexis Performance. A freely available Shiny web app using R is provided to make the proposed methodology accessible to other researchers and practitioners.

KEYWORDS
distinct-path, embedded regimes, generalized odds-ratio, response-rate, sample size, shared-path, SMART+

1 INTRODUCTION

Personalized treatments constitute an increasingly important theme in today’s health science. Dynamic treatment regimes (DTRs) offer a vehicle to operationalize personalized interventions in time-varying settings.\(^{1-3}\) They are often used in the management of chronic conditions where a subject is typically treated at multiple stages, for example, alcohol and drug abuse, tobacco addiction, diabetes, cancer, HIV infection, and mental illnesses.\(^{4-11}\) Precisely, DTRs are decision rules that recommend sequences of actions based on an individual’s treatment and covariate history. Once constructed based on data, these rules can be employed to optimize the health outcome, depending on the individual’s history.
Sequential multiple assignment randomized trial (SMART) is a special kind of clinical trial that provides high-quality data for comparing or constructing DTRs; the data from such trials are less vulnerable to causal confounding than longitudinal observational data. Methodological research on SMARTs has been on the rise in recent years, in accordance with the increasing prevalence of SMART or similar designs in practice, for example, in cancer, chronic periodontitis, health behavior change, and substance abuse, to mention a few. SMART designs involve randomization of individuals to available intervention options at an initial stage, followed by re-randomizations at each subsequent stage of some or all of the individuals to intervention options available at that stage. The re-randomizations and the set of intervention options at each stage may depend on information collected in prior stages such as how well the individual responded to the previous intervention(s). These designs attempt to conform better to the clinical practice, but still retain the well-known advantages of randomization over observational studies.

Various outcome types have been considered in the SMART design literature. For example, both Lavori and Dawson and Murphy considered primary analysis of SMART design with continuous outcomes; details about related sample size calculations under a variety of research questions were given by Oetting et al. These sample size calculations were further extended by different researchers to cover binary outcomes, noninferiority and equivalence SMART, pilot SMART, and SMART pilot. Binary outcomes from a SMART were analyzed previously via likelihood-based methods and recently a new simple data analytic approach was also proposed. A lot of attention in the literature was focused on analysis of survival outcomes in a SMART and associated sample size calculations. Composite outcomes were also considered. However, to the best of our knowledge, the literature on methods for analyzing ordinal outcomes in a SMART design till date is quite sparse, even though the outcomes of interest in many clinical and behavioral settings are measured in an ordinal scale and the methodologies to analyze such data in non-SMART context are available for decades for example. The need for analysis methods to deal with ordinal outcomes in a SMART design has been acknowledged by researchers for a long time. Zhao et al proposed a classification-based optimization method that may be used to estimate optimal DTRs of ordinal outcomes, however the method was for analyzing observational data rather than SMART data. Our method is vastly different, whereby we employ an ordinal measure of association, the generalized odds ratio (GOR), that is interpretable and easy to use for practitioners. We will defer the explanation of GOR to a later section.

1.1 SMART+ study: Digital approach to improving carbohydrate periodization behaviors in athlete

Our work has been motivated by the digital approach to improving carbohydrate periodization behaviors in athlete (SMART+) study conducted in the UK, via a menu planner mobile application, Hexis Performance (Figure 1).
Carbohydrate periodization, also known as fueling for the work required, is the carbohydrate availability adjusted in accordance with the demands of the specific training session to be completed, to optimize training performance.29 Despite the knowledge on what and when to eat, athletes usually struggle to adhere to the behavior, and often needs highly personalized support from nutrition coaches.30 As part of the study to reduce the need for expensive coaching support, a 4-week pilot three-stage SMART was conducted to evaluate the feasibility of developing a DTR around the mobile application (App), where the nutrition coach (NC) communicates with the athletes only when necessary (at stage 2 and/or stage 3) depending on their engagement rates (response) on the App. The full SMART design used is shown in Figure 2, wherein all athletes received the App and were randomized at stage 1 to either follow a relaxed or stringent response criteria for the rest of the trial. The full three-stage SMART design, with 16 embedded DTRs, is described by Yan et al.28

The current study aims to assess feasibility, as such the primary outcomes focused on app and coaching uptake rates, and estimating the carbohydrate periodization success rates; there is less concern in formally comparing the clinical outcomes among the embedded regimes in the design. In this study, the clinical outcomes are carbohydrate periodization behavior ranking, carbohydrate periodization behavior efficacy and belief about consequences, which are of ordinal nature, for example, the carbohydrate periodization behavior ranking ranks athletes as 1 (not periodizing at all), 2 (periodizing energy/kcal only) or 3 (periodizing both energy/kcal and carbohydrates). If the study is to follow-up with a confirmatory trial, it is necessary to formally compare the regimes. However, existing methods are not tailored to compare any two embedded regimes in a SMART design with respect to ordinal outcomes. The methodologies developed in this article will help to investigate such research questions properly; see Section 7 for further details.

For simplicity of this article, we describe the trial as a two-stage design (the more conventional design) by ignoring the third stage, that is, up to stage 2 in Figure 2. An athlete assigned to the relaxed response criteria was defined as a responder after one week, if their engagement was for at least 1 day in that week, and a nonresponder otherwise. For an athlete assigned to the stringent response criteria, the engagement had to be for at least 2 days in that week to be classified as a responder. Responders continued with the App, and nonresponders were randomized to either continue with App alone or support with NC (App + NC) for the second week (stage 2). As such there are four embedded

![Figure 2](image-url)
Table 1: Four dynamic treatment regimes (DTRs) embedded in the SMART.

| DTR | Stage 1 Intervention | Response Status | Stage 2 Intervention | Notation |
|-----|----------------------|-----------------|----------------------|----------|
| \(d^{(1)}\) | App + Relaxed | Yes \((R_s = 1)\) | App + Relaxed | \((\text{App + Relaxed})\) |
|      | No \((R_s = 0)\) |                | App + NC + Relaxed  | \((\text{App + Relaxed})^R \cdot (\text{App + NC + Relaxed})^{1-R_s}\) |
| \(d^{(2)}\) | App + Relaxed | Yes \((R_s = 1)\) | App + Relaxed | \((\text{App + Relaxed})\) |
|      | No \((R_s = 0)\) |                | App + Relaxed  | \((\text{App + Relaxed})^R \cdot (\text{App + Relaxed})^{1-R_s}\) |
| \(d^{(3)}\) | App + Stringent | Yes \((R_s = 1)\) | App + Stringent | \((\text{App + Stringent})\) |
|      | No \((R_s = 0)\) |                | App + NC + Stringent | \((\text{App + Stringent})^R \cdot (\text{App + NC + Stringent})^{1-R_s}\) |
| \(d^{(4)}\) | App + Stringent | Yes \((R_s = 1)\) | App + Stringent | \((\text{App + Stringent})\) |
|      | No \((R_s = 0)\) |                | App + Stringent  | \((\text{App + Stringent})^R \cdot (\text{App + Stringent})^{1-R_s}\) |

DTRs (see Table 1): \(d^{(1)}\): \((\text{App + Relaxed}) \cdot (\text{App + Relaxed})^R \cdot (\text{App + NC + Relaxed})^{1-R_s}\), \(d^{(2)}\): \((\text{App + Relaxed}) \cdot (\text{App + Relaxed})^R \cdot (\text{App + NC + Relaxed})^{1-R_s}\), \(d^{(3)}\): \((\text{App + Stringent}) \cdot (\text{App + Stringent})^R \cdot (\text{App + NC + Stringent})^{1-R_s}\), and \(d^{(4)}\): \((\text{App + Stringent}) \cdot (\text{App + Stringent})^R \cdot (\text{App + Stringent})^{1-R_s}\). where \(R_s\) and \(R_r\) are the response indicators corresponding to the relaxed and stringent response criteria (i.e., \(R_s = 1\) and \(R_r = 1\) if engagement rates are \(\geq 1\) day and \(\geq 2\) days), respectively. For example, an athlete consistent with \(d^{(1)}\) follows the regime “give App to the athlete, if the athlete had no engagement with the App after one week, support App with NC in the second week, else continue with App”. It is worth noting that, although the athletes may receive the same intervention, the experience for individuals can be very different depending on their responses, for example, a responder and a nonresponder to stage 1 may both receive the App only at stage 2. Note that among the above four regimes, both \(d^{(1)}\) and \(d^{(2)}\) start with the same initial intervention \(\text{App + Relaxed}\), and thus the responders at the first stage to \(\text{App + Relaxed}\) are “shared” between both these regimes. We call \(d^{(1)}\) and \(d^{(2)}\) shared-path DTRs. Similarly, \(d^{(3)}\) and \(d^{(4)}\) constitute another pair of shared-path DTRs. In contrast, \((d^{(1)}, d^{(3)})\), \((d^{(1)}, d^{(4)})\), \((d^{(2)}, d^{(3)})\) and \((d^{(2)}, d^{(4)})\) are pairs of distinct-path DTRs embedded in this design, as the elements within each pair start with different initial interventions and thus do not share any common group of trial participants.

1.2 Generalized odds ratio

A simple yet useful approach to compare ordinal outcomes across two or more groups utilizes a key quantity called the generalized odds ratio (GOR), first introduced by Agresti and later employed in the context of standard two-group randomized controlled trials. As the name suggests, the GOR is a generalization of the usual odds ratio for binary data, for example, in case of contingency tables and logistic regression. Our key contribution in the current article is to generalize the notion of GOR to more than one stages of the grouping variable (e.g., intervention) that can be applicable to a SMART design.

The main difference between Agresti’s GOR and our newly proposed version is the presence of the response rate to the initial intervention within the definition of the odds ratio type quantity (note that these response rates can be different for different embedded regimes). We first present the general framework for GOR using potential outcomes in Section 2. Interestingly, the comparison between distinct-path regimes and that between shared-path regimes call for different considerations; hence we deal with these two cases separately in Sections 3.1 and 3.2. In Section 4, we provide a likelihood based estimation of GOR, and a sample size calculation formula is given in Section 4.1. We further present two alternatives to estimate GOR in Section 5, and highlight the broader scope of GOR, where it can also be computed for continuous outcomes using, for example, U-statistics. The fact that GOR is not restricted to ordinal outcomes opens up the possibility to compare DTRs beyond the standard methods based on mean outcomes or value functions. Section 6 shows the performance of the GOR using simulation studies. Finally, we apply our proposed methodology to the SMART+ data in Section 7 and conclude the article with a discussion in Section 8. To facilitate wide dissemination, we have also developed a Shiny web app implementing the methodology, which is freely available online (https://www.iitg.ac.in/pgapps/dGOR/). In addition, in the Supplementary Material, we extend the proposed methodology to a general K-stage SMART.
2 | A GENERAL FRAMEWORK FOR COMPARING DTRS WITH ORDINAL OUTCOMES

Let $Y_1$ and $Y_2$ be two ordinal random variables, denoting the primary outcomes corresponding to two different groups (e.g., two intervention arms of a randomized controlled trial, RCT), each taking values in $J$ distinct ordered categories, say, $1, \ldots, J$. Then the generalized odds ratio (GOR) between groups 2 and 1 is defined as $\text{GOR}_{(2,1)} = \frac{P(Y_2 > Y_1 | g_2)}{P(Y_2 < Y_1 | g_1)}$. The interpretation of $\text{GOR}_{(2,1)}$ is simple. Assuming that a higher category of the outcome variable is better, $\text{GOR}_{(2,1)} > 1$ indicates that the group 2 has a better outcome than group 1, and $\text{GOR}_{(2,1)} < 1$ indicates the other way round; finally $\text{GOR}_{(2,1)} = 1$ implies that there is no difference in outcomes between the two groups. In the following, we extend the generalized odds ratio (GOR) to allow us to compare DTRs embedded in a SMART with ordinal outcomes.

To formally define the GOR in the SMART context, we utilize the well-known potential outcomes framework. For notational convenience, we re-represent the interventions in Figure 2 with more general terms, such that the embedded DTRs are rewritten as: $d^{(1)} = (A, A^R, C^{1-R}), d^{(2)} = (A, A^R, D^{1-R}), d^{(3)} = (B, B^R, E^{1-R}),$ and $d^{(4)} = (B, B^R, F^{1-R})$, where $A, B, C, D, E$ and $F$ may be identical or different interventions, and $R_A$ and $R_B$ are the indicators of response (1 for responder, 0 for nonresponder) corresponding to the initial interventions $A$ and $B$, respectively. Let $T_1$ and $T_2$ generically denote the interventions given to the subjects at the first and second stages, respectively, with $T_1 \in \{A, B\}, T_2 \in \{A, C, D\}$ if $T_1 = A$, and $T_2 \in \{B, E, F\}$ if $T_1 = B$. Then, let $Y_{T_1T_2}$ be the potential outcome under the intervention sequence $(T_1, T_2)$. Note that with respect to Figure 2 (up to two stages), there are only six potential outcomes, namely, $Y_{AA}, Y_{AC}, Y_{AD}, Y_{BE}, Y_{BE}$ and $Y_{BB}$. Then the potential outcome under any DTR in the current setup can be written in terms of the above six potential outcomes, as shown below.

Consider the longitudinal data trajectory $(O_1, T_1, O_2, T_2, Y)$ corresponding to an individual subject participating in a SMART, where $O_k$ denotes the pre-intervention observations at stage $k (k = 1, 2)$, $T_k$ is the intervention given at stage $k (k = 1, 2)$ as defined before, and $Y$ is the primary outcome measured at the end of the second stage. Furthermore, define the history variables as $H_1 = O_1$ and $H_2 = (O_1, T_1, O_2)$. Note that the response indicator $R_{T_1}$ can be subsumed in $O_2$ ($R_{T_1}$ can be either a component or a low-dimensional summary of the vector-valued $O_2$). For example, in the SMART+ study, $O_2$ is the number of days of engagement for that week. $R_{T_1}$ is an indicator for whether $O_2$ satisfies the relaxed or stringent response criteria following $T_1$ (i.e., at least 1 day and 2 days of engagement for athlete following $T_1 = \text{App + Relaxed}$ and $T_1 = \text{App + Stringent}$, respectively), and $Y$ is the carbohydrate periodization behavior ranking. Any arbitrary DTR $g$ with respect to the above data structure can be defined as a vector of decision rules, $g = (g_1, g_2)$, where $g_1(H_1) \in A_1$ and $g_2(H_2) \in A_2$, with $A_k$ denoting the class of intervention options at stage $k (k = 1, 2)$. Then the potential outcome under the arbitrary DTR $g$ can be defined as $Y_g = Y_{AA}(g_1(H_1) = A, g_2(H_2) = A) + Y_{AC}(g_1(H_1) = A, g_2(H_2) = C) + Y_{AD}(g_1(H_1) = A, g_2(H_2) = D) + Y_{BE}(g_1(H_1) = B, g_2(H_2) = B) + Y_{BE}(g_1(H_1) = B, g_2(H_2) = E) + Y_{BB}(g_1(H_1) = B, g_2(H_2) = B)$, where $I(\cdot)$ is an indicator function. Now we are in a position to define $\text{GOR}$ as follows. Let $Y_g$ and $Y_{g'}$ denote the potential outcomes under two dynamic regimes $g$ and $g'$, respectively. Then the generalized odds ratio (GOR) between $g$ and $g'$, denoted $\eta_{gg'}$, is defined as

$$\eta_{gg'} = \frac{P(Y_g > Y_{g'})}{P(Y_g < Y_{g'})},$$

where $P(Y_g > Y_{g'})$ is the probability that the outcome for a randomly selected subject from the set of subjects whose intervention sequence is consistent with the regime $g$ is larger than the outcome for a randomly selected subject from the set of subjects whose intervention sequence is consistent with the regime $g'$.

3 | COMPARISON OF TWO EMBEDDED DYNAMIC REGIMES

3.1 | Definition and properties of GOR for comparing distinct-path regimes

Suppose we are interested in comparing two distinct-path embedded dynamic regimes $d^{(1)} = (A, A^R, C^{1-R})$ and $d^{(3)} = (B, B^R, E^{1-R})$. This would be equivalent to $d^{(1)} = (\text{App + Relaxed}, \text{App + Relaxed})^R, (\text{App + NC + Relaxed})^{1-R}$ and $d^{(3)} = (\text{App + Stringent}, \text{App + Stringent})^R, (\text{App + NC + Stringent})^{1-R}$ as previously described in Section 1. In the current
context, it turns out that \( R_A = I(d_1(1)(H_1) = d_2(1)(H_2) = A) \) and \( R_B = I(d_1(2)(H_1) = d_2(2)(H_2) = B) \). Also, let \( Y_{d_3} \) denotes the primary outcome of a randomly selected subject from the set of subjects whose intervention sequence is consistent with the regime \( d_1 \). Similarly, \( Y_{d_3} \) denotes the same corresponding to the regime \( d_3 \). Then, 

\[
P(Y_{d_3} > Y_{d_1}) = \sum_{R_A, R_B \in \{0, 1\}} \sum_{u=1}^{J-1} \sum_{j=1}^{J} \delta_{\gamma_A} (1 - \gamma_A)^{1-R_A} (1 - \gamma_B)^{1-R_B} \pi_{AA} \pi_{BB} \epsilon^{1-R_A} \epsilon^{1-R_B},
\]

where \( u \) corresponds to the response category of the regime \( d_1 \) and \( s \) corresponds to the same for the regime \( d_3 \). Note that, for nonresponder) for the two randomly selected subjects from the regimes \( d_1 \) and \( d_3 \), 

\[
\eta_{DP}^{d_3, d_1} = \frac{\sum_{R_A, R_B \in \{0, 1\}} \sum_{u=1}^{J-1} \sum_{j=1}^{J} \delta_{\gamma_A} (1 - \gamma_A)^{1-R_A} (1 - \gamma_B)^{1-R_B} \pi_{AA} \pi_{BB} \epsilon^{1-R_A} \epsilon^{1-R_B}}{\sum_{R_A, R_B \in \{0, 1\}} \sum_{u=1}^{J-1} \sum_{j=1}^{J} \delta_{\gamma_A} (1 - \gamma_A)^{1-R_A} (1 - \gamma_B)^{1-R_B} \pi_{AA} \pi_{BB} \epsilon^{1-R_A} \epsilon^{1-R_B}},
\]

where the superscript “DP” indicates that the two regimes under comparison are distinct-path regimes. Note that, for \( J = 2 \), that is, for binary outcome data, the above expression boils down to 

\[
\eta_{DP}^{d_3, d_1} = \frac{\sum_{R_A, R_B \in \{0, 1\}} \sum_{u=1}^{J-1} \sum_{j=1}^{J} \delta_{\gamma_A} (1 - \gamma_A)^{1-R_A} (1 - \gamma_B)^{1-R_B} \pi_{AA} \pi_{BB} \epsilon^{1-R_A} \epsilon^{1-R_B}}{\sum_{R_A, R_B \in \{0, 1\}} \sum_{u=1}^{J-1} \sum_{j=1}^{J} \delta_{\gamma_A} (1 - \gamma_A)^{1-R_A} (1 - \gamma_B)^{1-R_B} \pi_{AA} \pi_{BB} \epsilon^{1-R_A} \epsilon^{1-R_B}},
\]

which is simply the odds ratio (OR) for SMART data. The expression (3) can further reduce to the conventional odds ratio, \( \pi_{AC,1} / \pi_{AC,2} \), only when there is no split of trial subjects according to their response/nonresponse statuses at the end of stage 1; such a situation arises in a SMART involving smoking cessation interventions. 

Note that, \( \eta_{DP}^{d_3, d_1} \) in (2) can be alternatively defined as 

\[
\eta_{DP}^{d_3, d_1} = \frac{\sum_{R_A, R_B \in \{0, 1\}} \sum_{u=1}^{J-1} \sum_{j=1}^{J} \delta_{\gamma_A} (1 - \gamma_A)^{1-R_A} (1 - \gamma_B)^{1-R_B} \pi_{AA} \pi_{BB} \epsilon^{1-R_A} \epsilon^{1-R_B}}{\sum_{R_A, R_B \in \{0, 1\}} \sum_{u=1}^{J-1} \sum_{j=1}^{J} \delta_{\gamma_A} (1 - \gamma_A)^{1-R_A} (1 - \gamma_B)^{1-R_B} \pi_{AA} \pi_{BB} \epsilon^{1-R_A} \epsilon^{1-R_B}},
\]

where the column vector \( \Pi'_{T_{1}T_{2}T_{2}} \) denotes the same corresponding to the regime \( d_1 \). Similarly, \( \Pi'_{T_{1}T_{2}T_{2}} \) and \( \Pi'_{BB} \) denote the upper triangular part, the lower triangular part and the diagonal part of a square matrix \( \Pi'_{BB} \) after replacing other elements by zeros, respectively. For example, 

\[
Z = \begin{bmatrix} a & b & c \\ d & e & f \\ g & h & i \end{bmatrix} \text{ implies } U(Z) = \begin{bmatrix} a & b & 0 \\ 0 & e & f \\ 0 & 0 & i \end{bmatrix} \text{ and } \text{diag}(Z) = \begin{bmatrix} a & 0 & 0 \\ 0 & e & 0 \\ 0 & 0 & i \end{bmatrix}.
\]

The expression of \( \eta_{DP}^{d_3, d_1} \) in (4) is computationally easier to work with.

### 3.2 Definition and properties of GOR for comparing shared-path regimes

In this section, we are interested in comparing two shared-path dynamic regimes, using the same notations as in Section 3.1. Consider two embedded shared-path regimes \( d_1 : (A, A, A^C \cdots A) \) and \( d_2 : (A, B^C \cdots B) \). Here, \( R_A = I(d_1(1)(H_1) = d_2(1)(H_2) = A) \) and \( R_B = I(d_1(2)(H_1) = d_2(2)(H_2) = B) \) denote the response indicators (1 for responder, 0 for nonresponder) for the two randomly selected subjects from the regimes \( d_1 \) and \( d_2 \), respectively. A shared-path
example from the SMART+ study is \( d^{(1)} : \{\text{App + Relaxed, App + Relaxed}\}^R \{\text{App + NC + Relaxed}\}^{1-R} \) and \( d^{(2)} : \{\text{App + Relaxed, App + Relaxed}\}^R \{\text{App + Relaxed}\}^{1-R} \). Also, let \( Y_{d^{(1)}} \) and \( Y_{d^{(2)}} \) denote their primary outcomes. Now we have,

\[
P(Y_{d^{(2)}} > Y_{d^{(1)}}) = \sum_{R_i, R'_i \in \{0,1\}} \sum_{u=1}^{J_i} \sum_{j=1}^{J_i} Y_{A}^{R_i + R'_i} (1 - Y_{A})^{2-R_i - R'_i} \times \Pi_{AA}^{k_A} c_{i} \times \Pi_{AD}^{k_D} d_{i}^{(1)} \times \Pi_{AC}^{k_C} c_{i}^{(1)}.
\]

Similarly \( P(Y_{d^{(2)}} < Y_{d^{(1)}}) \) can be computed. Hence, from (1) the GOR is given by

\[
\eta_{SP}^{d^{(2)}, d^{(1)}} = \frac{\sum_{R_i, R'_i \in \{0,1\}} \sum_{u=1}^{J_i} \sum_{j=1}^{J_i} Y_{A}^{R_i + R'_i} (1 - Y_{A})^{2-R_i - R'_i} \times \Pi_{AA}^{k_A} c_{i} \times \Pi_{AD}^{k_D} d_{i}^{(1)} \times \Pi_{AC}^{k_C} c_{i}^{(1)}}{\sum_{R_i, R'_i \in \{0,1\}} \sum_{u=2}^{J_i} \sum_{j=2}^{J_i} Y_{A}^{R_i + R'_i} (1 - Y_{A})^{2-R_i - R'_i} \times \Pi_{AA}^{k_A} c_{i} \times \Pi_{AD}^{k_D} d_{i}^{(1)} \times \Pi_{AC}^{k_C} c_{i}^{(1)}}, \tag{5}
\]

where the superscript “SP” indicates that the two regimes under comparison are shared-path regimes. The GOR, \( \eta_{SP}^{d^{(2)}, d^{(1)}} \) given in (5) to compare two shared-path regimes is a special case of the GOR, \( \eta_{DP}^{d^{(2)}, d^{(1)}} \) defined in (2); \( \eta_{SP}^{d^{(2)}, d^{(1)}} \) can be obtained from the \( \eta_{DP}^{d^{(2)}, d^{(1)}} \) by replacing \( d^{(3)} \), \( Y_{B} \) and \( R_{B} \) by \( d^{(2)} \), \( Y_{A} \) and \( R'_{A} \), respectively. Note that \( \eta_{SP}^{d^{(2)}, d^{(1)}} \) in (5) can be alternatively defined as

\[
\eta_{SP}^{d^{(2)}, d^{(1)}} = \frac{\sum_{R_i, R'_i \in \{0,1\}} \gamma_{A}(R_{A}, R'_{A}) \left[ \left( U \left( \Pi_{AA}^{k_A} c_{i} \times \Pi_{AD}^{k_D} d_{i}^{(1)} \times \Pi_{AC}^{k_C} c_{i}^{(1)} \right) - \text{diag} \left( \Pi_{AA}^{k_A} c_{i} \times \Pi_{AD}^{k_D} d_{i}^{(1)} \times \Pi_{AC}^{k_C} c_{i}^{(1)} \right) \right) \right]}{\sum_{R_i, R'_i \in \{0,1\}} \gamma_{A}(R_{A}, R'_{A}) \left[ \left( U \left( \Pi_{AA}^{k_A} c_{i} \times \Pi_{AD}^{k_D} d_{i}^{(1)} \times \Pi_{AC}^{k_C} c_{i}^{(1)} \right) - \text{diag} \left( \Pi_{AA}^{k_A} c_{i} \times \Pi_{AD}^{k_D} d_{i}^{(1)} \times \Pi_{AC}^{k_C} c_{i}^{(1)} \right) \right) \right]}.
\]

where \( \gamma_{A}(R_{A}, R'_{A}) = Y_{A}^{R_{A} + R'_{A}} (1 - Y_{A})^{2-R_{A} - R'_{A}} \).

Note that, \( \Pi_{AC} = \Pi_{AD} \) implies \( \eta_{SP}^{d^{(2)}, d^{(1)}} = 1 \). However, the converse is not true. We illustrate this point with the following example. Let \( \Pi_{AA} = (0.2, 0.3, 0.5) \), \( \Pi_{AC} = (0.12, 0.32, 0.56) \), \( \Pi_{AD} = (0.06, 0.41, 0.53) \) and \( Y_{A} = 0.2 \), here GOR = 1 even though \( \Pi_{AC} \neq \Pi_{AD} \). Also, \( \eta_{SP}^{d^{(2)}, d^{(1)}} \) is not invariant in \( \Pi_{AA} \). Consider two values of \( \Pi_{AA} \) as (0.5, 0.4, 0.1) and (0.2, 0.4, 0.4). It can be shown that for \( Y_{A} = 0.2 \), \( \eta_{SP}^{d^{(2)}, d^{(1)}} \) values are different in two cases (0.43 and 0.45) when both \( \Pi_{AC} \) and \( \Pi_{AD} \) are fixed at (0.3, 0.3, 0.4) and (0.6, 0.2, 0.2), respectively.

4 | MAXIMUM LIKELIHOOD ESTIMATION OF GOR

We assume that the usual assumptions about potential outcomes in a longitudinal setting, namely, (i) consistency, (ii) no unmeasured confounding and (iii) positivity, hold.\(^{33,34}\) Specifically, the consistency assumption states that the potential outcome under the observed intervention sequence and the observed outcome agree, that is, \( Y = Y_{T,T} \) if the observed intervention sequence is indeed \( (T_1, T_2) \). Thus, while the GOR is defined conceptually using potential outcomes, it can be computed based on observed data. On the other hand, the no unmeasured confounding assumption states that intervention allocation is independent of future potential outcomes given the history; this is satisfied by design in case of SMARTs.\(^{13}\) The positivity assumption states that an individual has a positive probability of receiving any of the intervention sequences considered in the study. Thus, by positivity assumption, at least some individuals receive each of the possible intervention sequences \( (T_1, T_2) \) feasible in the study.

The maximum likelihood estimate of \( \eta_{DP}^{d^{(2)}, d^{(1)}} \), say \( \hat{\eta}_{DP}^{d^{(2)}, d^{(1)}} \), can be computed by plugging-in the maximum likelihood estimates of \( \gamma_{S} \) (empirical response rates) and \( \pi_{S} \) (empirical probabilities of outcome categories) obtained from the data likelihood (see the Supplementary Material, Section 3). The asymptotic distribution of estimated GOR in (2) is given by

\[
\sqrt{N} \left( \hat{\eta}_{DP}^{d^{(2)}, d^{(1)}} - \eta_{DP}^{d^{(2)}, d^{(1)}} \right) \rightarrow \text{Normal} \left( 0, \sigma_{\hat{\eta}_{DP}^{d^{(2)}, d^{(1)}}}^2 \right), \tag{6}
\]
where $N^{-1} \sigma_{d_{i,j}^{(1)}}^2$ is the variance of $\hat{\eta}_{d_{i,j}^{(1)}}^{DP}$, with $N$ being the total number of subjects in the trial. See the Supplementary Material for detailed derivation. Using delta method, we have

$$\sqrt{N} \left( \log \hat{\eta}_{d_{i,j}^{(1)}}^{DP} - \log \hat{\eta}_{d_{i,j}^{(1)}}^{SP} \right) \rightarrow \text{Normal} \left( 0, \sigma_{d_{i,j}^{(1)}}^2 \right).$$

(7)

For small $N$, use of (7) is preferable. The maximum likelihood estimate of $\hat{\eta}_{d_{i,j}^{(1)}}^{SP}$, say $\hat{\eta}_{d_{i,j}^{(1)}}^{SP}$, can be computed by plugging-in the maximum likelihood estimates of $\gamma S$ and $\alpha S$, as before. The asymptotic distribution is given by

$$\sqrt{N} \left( \hat{\eta}_{d_{i,j}^{(1)}}^{SP} - \eta_{d_{i,j}^{(1)}}^{SP} \right) \rightarrow \text{Normal} \left( 0, \sigma_{d_{i,j}^{(1)}}^2 \right),$$

(8)

where $N^{-1} \sigma_{d_{i,j}^{(1)}}^2$ is the variance of $\hat{\eta}_{d_{i,j}^{(1)}}^{SP}$. See the Supplementary Material for detailed derivation. Using delta method, we have

$$\sqrt{N} \left( \log \hat{\eta}_{d_{i,j}^{(1)}}^{SP} - \log \hat{\eta}_{d_{i,j}^{(1)}}^{SP} \right) \rightarrow \text{Normal} \left( 0, \sigma_{d_{i,j}^{(1)}}^2 \right).$$

(9)

As noted in the Supplementary Material (see Section 11), the expressions of the asymptotic variance of the distinct-path ($d_{(3)}^{(1)}$ vs. $d_{(1)}^{(1)}$) and that of the shared-path ($d_{(2)}^{(1)}$ vs. $d_{(1)}^{(1)}$) comparison are the same if we replace $d_{(3)}^{(1)}$ by $d_{(2)}^{(1)}$, BB by AA and BE by AD. However, the derivation is different for the shared-path comparison compared to the distinct-path comparison of two regimes.

### 4.1 Primary analysis and sample size formula

Specifying a primary analysis is necessary for powering a SMART. If the current pilot SMART+ study were to proceed as a full-fledged SMART, a reasonable primary analysis would be to test if the regime $d_{(3)}^{(1)}$ differs from the regime $d_{(1)}^{(1)}$ in terms of the ordinal primary outcome (comparison of distinct-path embedded regimes). Consider the null hypothesis $H_0 : \eta_{d_{i,j}^{(1)}}^{DP} = 1$ against the alternative hypothesis $H_1 : \eta_{d_{i,j}^{(1)}}^{DP} = \delta$, where $\delta$ could take any positive or negative value. Using (6), we use $\hat{\eta}_{d_{i,j}^{(1)}}^{DP}$ as the test statistic for the primary analysis. For a positive (negative) value of $\delta$, the high (low) value of $\hat{\eta}_{d_{i,j}^{(1)}}^{DP}$ is an indication of departure from the null hypothesis. Let $z_{\alpha/2}$ be the $(1 - \alpha/2)$ percentile of the standard normal distribution and set the power of the test as $1 - \beta$, where $\beta$ is the type-II error. Using (6) the required sample size is given by $N = (z_{\alpha/2} + z_\beta)^2 \sigma_{d_{(2),d_{(1)}}^{(1)}}^2$. Here $N$ is the total number of subjects in the trial. We can consider $\delta / \sigma_{d_{(2),d_{(1)}}^{(1)}}$ as the standardized effect size, which can potentially be elucidated from scientific investigators prior to designing the SMART. The primary analysis and the sample size formula for the shared-path setup are similar to the above with replacement of $\hat{\eta}_{d_{i,j}^{(1)}}^{DP}$ and $\sigma_{d_{(2),d_{(1)}}^{(1)}}^2$ by $\hat{\eta}_{d_{i,j}^{(1)}}^{SP}$ and $\sigma_{d_{(2),d_{(1)}}^{(1)}}^2$, respectively.

### 5 ALTERNATIVE WAYS TO ESTIMATE GOR

#### 5.1 GOR based on concordant and discordant pairs

Goodman et al proposed a measure of association $\Gamma$ for an $I \times J$ cross-classified table, where $I$ and $J$ represent the number of ordinal categories of the row variable and the column variable, respectively. The Goodman-Kruskal $\Gamma$ is based on the number of concordant and discordant pairs corresponding to any two individuals randomly chosen from the population. Let the two chosen individuals be denoted by $(i, j)$ and $(i', j')$, where $i, i' = 1, \ldots, I$ and $j, j' = 1, \ldots, J$. The chosen pair is called concordant if $(i < i' \land j < j')$ or $(i > i' \land j > j')$ and discordant if $(i < i' \land j > j')$ or $(i > i' \land j < j')$. Note that, the GOR described in the current article is not defined for a $1 \times J$ cross-classified table; rather, we restrict to a $2 \times J$ table where the two rows denote two sub-populations (eg, two arms of an RCT) and the columns correspond to the $J$ ordered categories of an ordinal variable $Y$. We can then calculate GOR based on the number of concordant and discordant pairs in a slightly different manner. Suppose a randomly selected individual from the sub-population 1 is denoted by $(1, u)$ and that from the sub-population 2 is denoted by $(2, s); u, s = 1, \ldots, J$. Define the randomly selected pair to be concordant if $u < s$, that is, the individual selected from the sub-population 1 has a lower response category than the individual selected
from the sub-population 1, and discordant if \( u > s \). Thus, the total number of concordant and discordant pairs are given by 
\[
\sum_{j=1}^{J} \sum_{i=1}^{J} n_{iu} n_{js} \text{ and } \sum_{j=1}^{J} \sum_{i=1}^{J} n_{iu} n_{js},
\]
respectively, where \( n_{ij} \) denotes the cell frequency corresponding to the \( i \)th sub-population and the \( j \)th ordinal category with \( i = 1, 2; j = 1, \ldots, J \). One can estimate \( P(Y_2 > Y_1) \) by 
\[
\frac{1}{n_1 n_2} \sum_{j=1}^{J} \sum_{i=1}^{J} n_{iu} n_{js},
\]
where \( n_i = \sum_{j=1}^{J} n_{ij}, i = 1, 2 \) and thus can estimate \( GOR_{(2,1)} \) as the ratio of the total number of concordant pairs over the total number of discordant pairs as 
\[
\hat{GOR}_{(2,1)} = \frac{\sum_{i=1}^{J} \sum_{j=1}^{J} n_{ii} n_{jj}}{\sum_{i=1}^{J} \sum_{j=1}^{J} n_{ii} n_{jj}}.
\]

Similarly, for a SMART design, we can express the estimate of \( GOR \) defined in (2) as 
\[
\hat{GOR}_{(3,1)} = \frac{\sum_{i=1}^{J} \sum_{j=1}^{J} n_{AA,i} n_{BB,j} + 2 \times n_{AA,i} n_{BE,j} + 2 \times n_{AC,i} n_{BB,j} + 4 \times n_{AC,i} n_{BE,j}}{\sum_{i=1}^{J} \sum_{j=1}^{J} n_{AA,i} n_{BB,j} + 2 \times n_{AA,i} n_{BE,j} + 2 \times n_{AC,i} n_{BB,j} + 4 \times n_{AC,i} n_{BE,j}},
\]
where \( n_{AA,i} \) denotes the cell frequency of the \( i \)th ordinal category in the responder arm of the regime \( d^{(1)} \); other cell frequencies are defined accordingly. Note that, the total number of individuals in the responder branch of the regime \( d^{(1)} \) is \( n_{AA} = \sum_{i=1}^{J} n_{AA,i} = \frac{N}{2} \times \hat{\gamma}_A \), where \( N \) is the known total number of individuals in the entire SMART. In (10), the four components in the numerator (or the denominator) refer to the four different ways of choosing a pair of individuals from the two regimes \( d^{(1)} \) and \( d^{(3)} \). Specifically, we have the set as \{ \( AA \), \( BB \), \( AA \), \( BE \), \( AC \), \( BB \), \( AC \), \( BE \) \}, where \( AC \), \( BB \) refers to a pair wherein the first individual is randomly chosen from the nonresponder branch of the regime \( d^{(1)} \) and the second individual is randomly chosen from the responder branch of the regime \( d^{(3)} \). Intuitively, \( \hat{GOR}_{DP}^{(3,1)} \) is the ratio of the weighted sum of the concordances to the weighted sum of the discordances, where the weights are the inverse probability weights associated with a “restricted” SMART as in Figure 2.13,33,36 More specifically, the weight is a product of the number of times each of the selected two individuals in the pair is (evenly) randomized. For example, if the pair is coming from \( AC \), \( BB \), the weight is \( 2 \times 1 \) because the individual from the regime \( d^{(1)} \) is a nonresponder and hence randomized twice, whereas the one from the regime \( d^{(3)} \) is a responder and hence randomized only once. However, for the SMART design where both responders and nonresponders are evenly randomized (See Supplementary Material Figure 2), no such weighting is necessary.37 The use of the notion of concordance in the DTR literature is not entirely new; for example, concordance-assisted learning for optimal treatment regimes.38

5.2 \quad GOR for continuous outcomes based on U-statistic

The main focus of this article is to define and use \( GOR \) for comparing DTRs with ordinal outcomes. However, the \( GOR \) defined in (1) does not require \( Y_g \) and \( Y_{g'} \) to be ordinal variables. In fact, as discussed by Agresti in the context of two-grouped \( GOR \), the \( GOR \) can as well be used to compare DTRs based on continuous outcomes.25 Furthermore, the \( GOR \) defined in (1) does not assume any particular parametric model for the data. Thus the scope of \( GOR \) is very broad, and it provides an alternative approach to comparing DTRs beyond the standard methods based on mean potential outcomes or value functions; the value function of a regime \( g \) is defined as \( E(Y_g) \).32,39 Thus, while value-based methods work with mean potential outcomes, \( GOR \)-based methods work with stochastic ordering of potential outcomes.

We can write the \( GOR \) defined in (1) to compare the regimes \( d^{(3)} \) and \( d^{(1)} \) in Figure 2 with continuous outcome as 
\[
\hat{GOR}_{DP}^{(3,1)} = \frac{P(Y_g > Y_{g'})}{1 - P(Y_{g'} > Y_g)}
\]
Note that, the \( P(Y_g > Y_{g'}) \) can be estimated by using the \( U \)-statistic 
\[
\frac{1}{n_{d^{(3)}} n_{d^{(1)}}} \sum_{s=1}^{n_{d^{(3)}}} \sum_{u=1}^{n_{d^{(1)}}} \phi(Y_{d^{(3)}}, Y_{d^{(1)}}),
\]
where \( n_{d^{(3)}} \) and \( n_{d^{(1)}} \) denote the total number of individuals with intervention sequences consistent with the regimes \( d^{(3)} \) and \( d^{(1)} \), respectively; \( Y_{d^{(3)}} \) denotes the outcome of \( s \)th individual corresponding to the regime \( d^{(3)} \); and 
\[
\phi(Y_{d^{(3)}}, Y_{d^{(1)}}) = \sum_{R_B, R_A \in [0,1]} Y_{A,i} Y_{B,j} (1 - Y_{A,i})^{1 - R_A} (1 - Y_{B,j})^{1 - R_B} I\{Y_{BBRBE} > Y_{AA(i - 1) - s}, A \}
\]
where \( I\{\cdot\} \) is an indicator function; \( Y_{BE,s} \) denotes the outcome of \( s \)th individual with responder status \( R_B = 0 \) (ie, \( T_1, T_2 \) = \( B, E \)) corresponding to the regime \( d^{(3)} \). The \( U \)-statistic in (11) is a two-sample \( U \)-statistic with \( E(\phi(Y_{d^{(3)}}, Y_{d^{(1)}})) = P(Y_{d^{(3)}} > Y_{d^{(1)}}) \) and \( \phi(\cdot, \cdot) \) is symmetric by default as it contains only one argument from each of the two samples.
TABLE 2  Comparison of distinct-path regimes with an ordinal outcome. Here, \( \gamma_A = 0.3 \) and \( \gamma_B = 0.4 \), nominal power is 0.80 and type-I error rate is 0.05. The standardized effect size is in log-scale. Estimated powers and coverage probabilities are based on 5000 simulations.

| Serial number | \( \pi(A, A) \) | \( \pi(A, C) \) | \( \pi(B, B) \) | \( \pi(B, E) \) | Std. ES (log scale) | \( \hat{r}_{DP}^{\pi_1, \pi_2} \) | \( r_{DP}^{\pi_1, \pi_2} \) | SSE | ASE | power | \( \hat{C} \) |
|---------------|-----------------|-----------------|-----------------|-----------------|----------------------|--------------------------|--------------------------|-----|-----|-------|-----|
| 1             | (0.23, 0.51, 0.26) | (0.31, 0.50, 0.19) | (0.50, 0.41, 0.09) | (0.14, 0.47, 0.39) | 0.219 | 2.55 | 164 | 2.72 | 1.06 | 1.14 | 0.78 | 0.94 |
| 2             | (0.41, 0.23, 0.36) | (0.50, 0.22, 0.28) | (0.58, 0.20, 0.22) | (0.27, 0.22, 0.51) | 0.147 | 1.86 | 366 | 1.89 | 0.43 | 0.43 | 0.78 | 0.95 |
| 3             | (0.21, 0.40, 0.39) | (0.28, 0.41, 0.31) | (0.30, 0.41, 0.29) | (0.12, 0.34, 0.54) | 0.117 | 1.64 | 571 | 1.66 | 0.29 | 0.30 | 0.79 | 0.95 |
| 4             | (0.13, 0.22, 0.65) | (0.10, 0.19, 0.71) | (0.09, 0.18, 0.73) | (0.20, 0.26, 0.54) | -0.085 | 0.66 | 1096 | 0.67 | 0.10 | 0.10 | 0.78 | 0.95 |
| 5             | (0.12, 0.24, 0.64) | (0.09, 0.21, 0.70) | (0.07, 0.18, 0.75) | (0.18, 0.28, 0.54) | -0.099 | 0.61 | 797 | 0.61 | 0.12 | 0.11 | 0.82 | 0.95 |
| 6             | (0.28, 0.52, 0.20) | (0.34, 0.50, 0.16) | (0.08, 0.43, 0.49) | (0.20, 0.52, 0.28) | -0.161 | 0.50 | 305 | 0.53 | 0.26 | 0.16 | 0.81 | 0.94 |

6 | SIMULATION STUDIES

Before we apply the proposed methodologies to the SMART+ data, we present two thorough simulation studies to illustrate their performances. Specifically, Section 6.1 and 6.2 present the performance of the GOR-based estimation and inference in case of distinct-path and shared-path dynamic regimes, respectively (cf. Section 3); the details of the data generation process are described in the Supplementary Material. The response rates corresponding to initial interventions \( A \) and \( B \) are taken as \( \gamma_A = 0.3 \) and \( \gamma_B = 0.4 \), respectively. Simulations considering different values of the response rates are shown in the Supplementary Material. We set the type-I error rate at 0.05 and the nominal power at 0.80.

6.1 | Simulation study for distinct-path regimes

This section aims to assess the performance of \( \eta_{DP}^{\pi_1, \pi_2} \) in comparing two distinct-path embedded regimes \( \delta_1 \) and \( \delta_3 \) in a two-stage SMART. Taking the carbohydrate periodization behavior ranking in the SMART+ study for example, we consider the ordinal outcome \( Y \) with \( J = 3 \) categories in ascending order. For regime \( \delta_1 \), the cell probabilities of \( Y \) are given by \( \pi(A, A) = (\pi_{AA,1}, \pi_{AA,2}, 1 - \pi_{AA,1} - \pi_{AA,2}) \) for the responders and \( \pi(A, C) = (\pi_{AC,1}, \pi_{AC,2}, 1 - \pi_{AC,1} - \pi_{AC,2}) \) for the non-responders. Likewise, for regime \( \delta_3 \), the corresponding cell probabilities are \( \pi(B, B) = (\pi_{BB,1}, \pi_{BB,2}, 1 - \pi_{BB,1} - \pi_{BB,2}) \) for the responders and \( \pi(B, E) = (\pi_{BE,1}, \pi_{BE,2}, 1 - \pi_{BE,1} - \pi_{BE,2}) \) for the non-responders. The serial number in the first column of Table 2 shows six different scenarios. The first three of them correspond to \( \eta_{DP}^{\pi_1, \pi_2} > 1 \) and the last three correspond to \( \eta_{DP}^{\pi_1, \pi_2} < 1 \). Here \( \eta_{DP}^{\pi_1, \pi_2} \) denotes the true values of the corresponding population GOR. We obtain the true value of GOR \( \eta_{DP}^{\pi_1, \pi_2} \) by using Monte Carlo computation considering a “large” population of size of \( 10^6 \). Figure 3(a) shows the plot of barycentric coordinates of the probabilities from the six different scenarios in Table 2. Any three probabilities of the form \( (p_1, p_2, 1 - p_1 - p_2) \) can be represented by a unique point in an equilateral triangle in a barycentric coordinate system. Three vertices are denoted by \( (0, 0, 0), (0, 1, 0) \) and \( (0, 0, 1) \). In a barycentric coordinate plot, a point \((p_1, p_2, 1 - p_1 - p_2)\) can be located by considering (i) a distance \( p_1 \) from the opposite arm of the vertex \((0, 0, 0)\), (ii) a distance \( p_2 \) from the opposite arm of the vertex \((0, 0, 1)\), and, (iii) a distance \( 1 - p_1 - p_2 \) from the opposite arm of the vertex \((0, 0, 0)\). The objective of the Figure 3A is to show how the six simulation scenarios in Table 2 are distributed in the parameter space represented by the barycentric coordinate system.

In Table 2, the “Std.ES” denotes the standardized effect size which is calculated as \( \log \eta_{DP}^{\pi_1, \pi_2} \) divided by the square root of the variance of \( \log \eta_{DP}^{\pi_1, \pi_2} \); \( N \) denotes the estimated required sample size using the distribution of \( \log \eta_{DP}^{\pi_1, \pi_2} \). Based

\[ \pi(A, A) = (\pi_{AA,1}, \pi_{AA,2}, 1 - \pi_{AA,1} - \pi_{AA,2}) \]
Corresponding to Tables 2 and 3, the Barycentric plots of different multinomial probabilities for comparing (a) distinct-path regimes, \( \pi(A, A), \pi(A, C), \pi(B, B), \pi(B, E) \); and (b) shared-path regimes, \( \pi(A, A), \pi(A, C), \pi(A, D) \).

### Table 3
Comparison of shared-path regimes with an ordinal outcome. Here, \( \gamma_A = 0.3 \) and \( \gamma_B = 0.4 \), nominal power is 0.80 and type-I error rate is 0.05. The standardized effect size is in log-scale. Estimated powers and coverage probabilities are based on 5,000 simulations.

| Serial number | \( \pi(A, A) \) | \( \pi(A, D) \) | Std. ES (log scale) | \( \hat{\eta}^{SP}_{d_3,d_1} \) | \( \hat{\eta}^{SP}_{d_2,d_1} \) | SSE | ASE | power | \( \hat{CP} \) |
|---------------|----------------|----------------|---------------------|-----------------|-----------------|-----|-----|-------|---------|
| 1             | (0.24, 0.52, 0.24) |                | 0.160              | 1.88            | 1.94            | 0.44| 0.49| 0.77  | 0.97    |
| 2             | (0.63, 0.33, 0.04) | (0.38, 0.49, 0.13) | 0.160              | 1.88            | 1.94            | 0.44| 0.49| 0.77  | 0.97    |
| 3             | (0.03, 0.66, 0.31) |                | 0.148              | 1.96            | 1.97            | 0.54| 0.51| 0.77  | 0.94    |
| 4             | (0.19, 0.74, 0.07) | (0.07, 0.75, 0.18) | 0.148              | 1.96            | 1.97            | 0.54| 0.51| 0.77  | 0.94    |
| 5             | (0.43, 0.17, 0.40) |                | 0.109              | 1.56            | 1.60            | 0.26| 0.27| 0.81  | 0.96    |
| 6             | (0.73, 0.12, 0.15) | (0.56, 0.16, 0.28) | 0.109              | 1.56            | 1.60            | 0.26| 0.27| 0.81  | 0.96    |

| Serial number | \( \pi(A, A) \) | \( \pi(A, D) \) | Std. ES (log scale) | \( \hat{\eta}^{SP}_{d_3,d_1} \) | \( \hat{\eta}^{SP}_{d_2,d_1} \) | SSE | ASE | power | \( \hat{CP} \) |
|---------------|----------------|----------------|---------------------|-----------------|-----------------|-----|-----|-------|---------|
| 1             | (0.36, 0.36, 0.28) |                | 0.109              | 1.56            | 1.60            | 0.26| 0.27| 0.81  | 0.96    |
| 2             | (0.40, 0.35, 0.25) | (0.52, 0.32, 0.16) | -0.080             | 0.73            | 1.218           | 0.08| 0.09| 0.80  | 0.95    |
| 3             | (0.17, 0.10, 0.73) |                | -0.113             | 0.58            | 0.618           | 0.12| 0.12| 0.82  | 0.94    |
| 4             | (0.16, 0.32, 0.52) | (0.38, 0.35, 0.27) | -0.181             | 0.50            | 0.241           | 0.13| 0.14| 0.80  | 0.96    |

The 5,000 simulations, \( \hat{\eta}^{DP}_{d_3,d_1} \), is the estimated value of \( \eta^{DP}_{d_3,d_1} \); SSE is the sample standard error; ASE is the asymptotic standard error; \( \hat{\eta}^{SP}_{d_2,d_1} \), is the estimated power and \( \hat{CP} \) is the estimated coverage probability. In Table 2, \( \hat{\eta}^{DP}_{d_3,d_1} \), is close to its true value in all the six scenarios, indicating good estimation. The estimated required sample size \( N \) varies from 164 to 571 when \( \eta^{DP}_{d_3,d_1} > 1 \) and from 305 to 1096 when \( \eta^{DP}_{d_3,d_1} < 1 \). Note that, \( N \) is a decreasing function of the absolute value of the standardized effect size. However, we can have the same standardized effect size for different combinations of \( \eta^{DP}_{d_3,d_1} \), the response rates and the cell probabilities corresponding to the two regimes. The SSE and ASE are close to each other in all the scenarios. The estimated empirical powers and the coverage probabilities are close to their corresponding nominal values in all the cases.

#### 6.2 Simulation study for shared-path regimes

Here, we consider a simulation study to compare the shared-path regimes \( d^{(1)} \) and \( d^{(2)} \) that start with the same initial interventions as described in Section 1 and 3.2. As in the previous section, we set the number of categories of the ordinal outcome \( Y \) as \( J = 3 \) in ascending order. For regime \( d^{(2)} \), the cell probabilities of \( Y \) are given by \( \pi(A, A) = (\pi_{AA,1}, \pi_{AA,2}, 1 - \pi_{AA,1} - \pi_{AA,2}) \) for the responders and \( \pi(A, D) = (\pi_{AD,1}, \pi_{AD,2}, 1 - \pi_{AD,1} - \pi_{AD,2}) \) for the nonresponders. Note that, \( \pi(A, A) \)
corresponds to both regimes \(d^{(1)}\) and \(d^{(2)}\) (shared-path). The barycentric coordinate plot in Figure 3(b) shows how the six simulation scenarios in Table 3 are distributed in the barycentric coordinate system.

Table 3 shows the results of six scenarios for shared-path comparison of two regimes. As in Section 6.1, the first three scenarios correspond to \(\eta_{\text{SP}}^{d^{(2)},d^{(1)}} > 1\) and the last three scenarios to \(\eta_{\text{SP}}^{d^{(2)},d^{(1)}} < 1\). The estimated required sample size \(N\) ranges from 304 to 659 when \(\eta_{\text{SP}}^{d^{(2)},d^{(1)}} > 1\) and from 241 to 1218 when \(\eta_{\text{SP}}^{d^{(2)},d^{(1)}} < 1\). In all the six scenarios, the SSE and the ASE are close to each other. The estimated empirical powers and the coverage probabilities are close to their corresponding nominal values.

In summary, from both the simulation studies in Sections 6.1 and 6.2, it is evident that the proposed GORs for comparing both distinct-path and shared-path regimes perform well.

7 | APPLICATION TO SMART+ DATA

In this section, we demonstrate how the developed GOR can be used to compare any two different embedded regimes using the data in SMART+ study (N=87). Note the SMART+ sample size is small, as the study was not powered for formal comparison but as a feasibility trial. We will only consider up to two stages in Figure 2, as described in Section 1.1, and we shorthand the four embedded regimes as \(d(\text{App, NC, Relaxed}) = (\text{App + Relaxed}), (\text{App + Relaxed})^*, (\text{App + NC + Relaxed})^1_{-R}, d(\text{App, Relaxed}) = (\text{App + Relaxed}), (\text{App + Relaxed})^*, (\text{App + NC + Relaxed})^1_{-R}\), \(d(\text{App, NC, Stringent}) = (\text{App + Stringent}), (\text{App + Stringent})^*, (\text{App + NC + Stringent})^1_{-R}\), \(d(\text{App, Stringent}) = (\text{App + Stringent}), (\text{App + Stringent})^*, (\text{App + NC + Stringent})^1_{-R}\), where \(R_1\) and \(R_2\) are the response indicators (1/0) following the relaxed and stringent response criteria, respectively. An athlete with a relaxed or stringent response criteria needs to have an engagement rate of at least 1 day (i.e., low response threshold) or at least 2 days (i.e., high response threshold) on the App in one week, respectively, to be considered a responder. Note that it is possible to use the GOR for all three stages in Figure 2, using the extended methodology for general K-stage SMART as detailed in the Supplementary Material. Suppose we are interested in comparing clinical outcomes such as the carbohydrate periodization behavior ranking, an ordinal variable with the levels 1 (not periodizing at all), 2 (periodizing energy/kcal only) and 3 (periodizing both energy/kcal and carbohydrates); the carbohydrate periodization self-efficacy, a 3-item measure where each statement asks the athletes to rate their confidence level on “carbohydrate periodization”, “meal planning” and “adherence to plan”; from 1 (not confident at all), 2 (a little confident), 3 (moderately confident), 4 (quite confident) to 5 (very confident); and the belief about consequences, a 3-item measure about changing “health”, “performance”, and “body composition”, on a scale 1 (not at all), 2 (a confident), 3 (moderately), 4 (very much), and 5 (extremely).

In Table 4, we present comparisons between four different pairs of distinct-path regimes and two different pairs of shared-path regimes for carbohydrate periodization behavior ranking. Here, the interpretation of \(\text{GOR}_{2,1} = \frac{P(Y_{\text{Regime}}}^{(2)}> Y_{\text{Regime}}}^{(1)})/P(Y_{\text{Regime}}}^{(2)}< Y_{\text{Regime}}}^{(1)})\) is as follows: Regime\(^{(2)}\) is better than Regime\(^{(1)}\) if \(\text{GOR}_{2,1} > 1\), and worse if \(\text{GOR}_{2,1} < 1\); a GOR is significant, if the confidence intervals (CIs) do not contain 1. For the four different pairs of distinct-path regimes, we let any one of the \(d(\text{App, NC, Relaxed})\) and \(d(\text{App, Relaxed})\) be taken as Regime\(^{(1)}\), whereas any one of the \(d(\text{App, NC, Stringent})\) and \(d(\text{App, Stringent})\) can be considered as Regime\(^{(2)}\); and for the two pairs of shared-path regimes, we let the regimes with NC be Regime\(^{(2)}\), that is, \(d(\text{App, Relaxed})\) is considered as Regime\(^{(1)}\) when \(d(\text{App, NC, Relaxed})\) is taken as Regime\(^{(2)}\). Similarly, \(d(\text{App, Stringent})\) is the Regime\(^{(1)}\) when \(d(\text{App, NC, Stringent})\) is taken as Regime\(^{(2)}\).

Among the four distinct-path regimes comparisons in Table 4, regimes with stringent response criteria, \(d(\text{App, NC, Stringent})\) and \(d(\text{App, Stringent})\) perform worse than regimes with relaxed response criteria, with significantly inferior performance when compared to \(d(\text{App, NC, Relaxed})\) (\(\text{GOR}_{2,1} = 0.51\)) with (CI = 0.10, 0.92) and \(\text{GOR}_{2,1} = 0.48\) with CI = (0.08, 0.88), respectively. For the two different pairs of shared-path regimes comparisons, the regimes with NC, \(d(\text{App, NC, Relaxed})\) and \(d(\text{App, NC, Stringent})\), show potential superiority over their counterparts \(d(\text{App, Relaxed})\) and \(d(\text{App, Stringent})\), respectively, although they are not statistically significant (\(\text{GOR}_{2,1} = 1.31\)) with (CI = 0.47, 2.15) and \(\text{GOR}_{2,1} = 1.07\) with (CI = 0.45, 1.69), respectively. Based on these GORs, one can therefore infer that using a relaxed response criteria and supporting the App with a nutrition coach (NC) at stage 2 for nonresponders are better options. It is not surprising that the regimes with NC for nonresponders show better results than without NC. However, the finding that stringent response criteria is inferior to relaxed response criteria is contrary to expectation. One would normally expect that, under the stringent response criteria, athletes generally have higher chances of being assigned to receive additional support from NC early, as nonresponders (e.g., an athlete with 1 day engagement would be a nonresponder under the stringent response criteria, but a responder under the relaxed criteria), and hence improve their carbohydrate periodization behavior. This warrants further investigation into other aspects such as the third stage intervention in the design, the app
Comparison of regimes with carbohydrate periodization behavior ranking as the ordinal outcome in SMART+ data. The response rates are $\gamma_R = 0.64$ and $\gamma_S = 0.54$, following the first-stage intervention with “Relaxed” and “Stringent” response criteria, respectively. Note that, $GOR_{2,1} = P(Y_{\text{Regime}^2} > Y_{\text{Regime}^1}) / P(Y_{\text{Regime}^2} < Y_{\text{Regime}^1})$. The overall DTR probability, for each outcome value (0, 1, 2), represents the probability of getting that outcome given the DTR.

### Comparison of distinct-path regimes

| Regime$^{(1)}$ | Cell probabilities: | Cell probabilities: |
|---------------|---------------------|---------------------|
|               | (Responder)         | (Nonresponder)      |
|               | (Nonresponder)      |                     |
| [Overall DTR probabilities] |                     |                     |

| $d(App, NC, Relaxed)$ | (0.36, 0.36, 0.28) | $d(App, NC, Stringent)$ | (0.50, 0.27, 0.23) | 0.51 | (0.10, 0.92) |
|----------------------|---------------------|------------------------|-------------------|-------|------------|
|                      | (0.50, 0.12, 0.38)  |                        | (0.62, 0.38, 0)   |       |            |
|                      | [0.39, 0.3, 0.31]   |                        | [0.54, 0.31, 0.15]|       |            |

| $d(App, NC, Relaxed)$ | (0.36, 0.36, 0.28) | $d(App, Stringent)$   | (0.50, 0.27, 0.23)| 0.48 | (0.08, 0.88)|
|----------------------|---------------------|------------------------|------------------|-------|------------|
|                      | (0.50, 0.12, 0.38)  |                        | (0.67, 0.33, 0)  |       |            |
|                      | [0.39, 0.3, 0.31]   |                        | [0.54, 0.29, 0.17]|       |            |

| $d(App, Relaxed)$    | (0.36, 0.36, 0.28) | $d(App, NC, Stringent)$ | (0.50, 0.27, 0.23)| 0.67 | (0.12, 1.22)|
|----------------------|---------------------|------------------------|------------------|-------|------------|
|                      | (0.67, 0.17, 0.16)  |                        | (0.62, 0.38, 0)  |       |            |
|                      | [0.42, 0.32, 0.26]  |                        | [0.54, 0.31, 0.15]|       |            |

| $d(App, Relaxed)$    | (0.36, 0.36, 0.28) | $d(App, Stringent)$   | (0.50, 0.27, 0.23)| 0.63 | (0.10, 1.16)|
|----------------------|---------------------|------------------------|------------------|-------|------------|
|                      | (0.67, 0.17, 0.16)  |                        | (0.67, 0.33, 0)  |       |            |
|                      | [0.42, 0.32, 0.26]  |                        | [0.54, 0.29, 0.17]|       |            |

### Comparison of shared-path regimes

| $d(App, Relaxed)$ | (0.36, 0.36, 0.28) | $d(App, NC, Relaxed)$ | (0.36, 0.36, 0.28)| 1.31 | (0.47, 2.15)|
|-------------------|--------------------|-----------------------|------------------|-------|------------|
|                   | (0.67, 0.17, 0.16) | (0.50, 0.12, 0.38)   | (0.39, 0.3, 0.31)|       |            |
|                   | [0.42, 0.32, 0.26] |                       | [0.54, 0.31, 0.15]|       |            |

| $d(App, Stringent)$ | (0.50, 0.27, 0.23) | $d(App, NC, Stringent)$ | (0.50, 0.27, 0.23)| 1.07 | (0.45, 1.69)|
|---------------------|--------------------|------------------------|------------------|-------|------------|
|                     | (0.67, 0.33, 0)   | (0.62, 0.38, 0)        | (0.54, 0.31, 0.15)|       |            |

Engagement over time during the trial, the messaging frequency and interaction quality between the nutrition coaches and the athletes, which are beyond the scope of this article. The analyses for the items in the carbohydrate periodization self-efficacy and belief about consequences are detailed in the Supplementary Material (Section 7). As sample size were small, we highlight again the results are more indicative for future confirmatory trial than definitive.

### 8 Discussion

The SMART is a very flexible design that is not limited to the structure in Figure 2. In Figure 2, responders are not re-randomized; Nahum-Shani et al refers to this type of SMARTs as a “restricted” SMART. There are also many other variations, such as the SMART where both responders and nonresponders are re-randomized (See Supplementary Material Figure 2) potentially to different interventions. The Supplementary Material (Section 8), outlines the GOR methodology tailored to a SMART design where the responders are also re-randomized at the second stage in the same way as the nonresponders. In this SMART design, there are eight embedded DTRs.

Note that the original intention of a SMART was specifically not to be confirmatory about DTRs. However, in recent times, SMART designs have become more popular and useful in different areas of science. While majority of SMARTs have
a developmental goal, some may have a confirmatory goal, for example, in comparative effectiveness trials as discussed by Lavori and Dawson.\textsuperscript{42} For example, in the M-bridge SMART, the required minimum sample size is based on the primary aim of examining the effect of adaptive prevention interventions (APIs) vs. assessment only on binge drinking (primary outcome) and negative drinking-related consequences and increased health services utilization (secondary outcomes).\textsuperscript{43} The APIs are the DTRs in our language.

As personal data collection becomes increasingly easy from mobile devices and sensors, the notion of developing DTRs and using SMARTs is progressively gaining traction across many areas of clinical sciences. In this context, we view the introduction of the generalized odds ratio (\textit{GOR}) as timely, as the demand for more specialised methodologies to deal with various types of SMART-related outcome measures (eg, binary, ordinal, continuous, composite, and survival) grows in conjunction with the increasing number of SMARTs in the field. The \textit{GOR} is a useful measure of association that is suitable for binary, ordinal and continuous outcomes from SMART. The \textit{GOR} is also easy to interpret as it is an extension of the simple odds ratio that is widely used in clinical and behavioral sciences. The connection between \textit{GOR} and U-statistic, as shown in Section 5.2, makes the \textit{GOR} useful for continuous outcomes. A freely available Shiny web app (https://www.iitg.ac.in/pgapps/dGOR/) using R is provided to make the proposed method accessible to other researchers and practitioners. The web app can perform the required sample size estimation, data analysis using only cell probabilities from a completed study, and data analysis from raw data in Excel format. The app can be used both for “restricted” SMARTs and for SMARTs where both responders and nonresponders are re-randomized.

Apparently, in the comparison of two shared-path DTRs, the difference can be seen due to the second stage treatment for nonresponders. However, if we do not consider the shared subgroup (responders) along with the response rate, we may end up with wrong conclusions. The following example illustrates the importance of considering the shared subgroup and the response rate (\(\gamma_d\)). Consider two shared-path DTRs, \(d^{(1)}\) : \((A,A,R_A\rightarrow C\rightarrow R_B)\), and \(d^{(2)}\) : \((A,A,R_A\rightarrow D\rightarrow R_B)\), indicating that in both regimes patients start with treatment A, then continue with treatment A if responder \((R_A = 1)\), and get switched to treatment C in \(d^{(1)}\) and to treatment D in \(d^{(2)}\) if nonresponder \((R_A = 0)\). Hypothetical cell probabilities corresponding to a three-category ordinal variable are given below for different legs (AA, AC, AD): Scenario 1: AA \(\rightarrow (0.8,0.1,0.1)\), AC \(\rightarrow (0.2,0.3,0.5)\), AD \(\rightarrow (0.5,0.3,0.2)\), with the total sample size in the SMART = 300, and \(\gamma_d = 0.1\). From this data, we have the estimated \textit{GOR}, \(\hat{\eta}_{SP,d^{(1)},d^{(2)}}\) = 0.34 with 95\% CI = (0.17, 0.51). Scenario 2: AA \(\rightarrow (0.8,0.1,0.1)\), AC \(\rightarrow (0.2,0.3,0.5)\), AD \(\rightarrow (0.5,0.3,0.2)\), with the total sample size in the SMART = 300, and \(\gamma_d = 0.9\). Here, we have \(\hat{\eta}_{SP,d^{(1)},d^{(2)}} = 0.85\) with 95\% CI = (0.63, 1.06). Scenario 3: AA \(\rightarrow (0.4,0.1,0.1)\), AC \(\rightarrow (0.2,0.3,0.5)\), AD \(\rightarrow (0.5,0.3,0.2)\), with the total sample size in the SMART = 300, and \(\gamma_d = 0.9\). In this scenario, \(\hat{\eta}_{SP,d^{(1)},d^{(2)}} = 0.89\) with 95\% CI = (0.75, 1.03). From the scenario 1 to 2, the only change was in the response rate, from 0.1 to 0.9. Because of that change, the \textit{GOR} changed from being significant to nonsignificant (the 95\% CI does not include 1 in the first scenario but does so in the second). Next, if we compare scenarios 1 and 3, where changes happen both in the AA cell probabilities and in the response rate, we observe the same phenomenon in terms of the significance of the estimated \textit{GOR}. However, in both cases, we have not changed the cell probabilities corresponding to the nonresponders’ legs AC and AD. Therefore, we conclude that, in the comparison of two shared-path DTRs, the consideration of the shared subgroup (eg, AA) is necessary which cannot be handled by using standard single-stage methods.

The \textit{GOR} specifically fills the literature gap in the estimation and comparison of embedded DTRs in SMARTs for ordinal outcomes. We highlight the value of providing this methodology by using the SMART+ study as an example. In the SMART+ study, the primary end-point was defined as the success in attaining carbohydrate periodization behavior, by collapsing the ordinal scale, such that 1 (not periodizing at all) and 2 (periodizing energy/kcal only) are considered failure (ie, success = 0) and 3 (periodizing both energy/kcal and carbohydrates) as success. Note that dichotomizing continuous or ordinal measures is a common yet problematic practice in clinical research; conventional studies, however, can work around this using well established methods, such as the standard \textit{GOR}.\textsuperscript{25,44} If we combine the outcome cell probabilities in Table 4 into two categories, success = 1/0 as defined earlier, the regime \(d(\text{App, NC, Stringent})\) will be identical to \(d(\text{App, NC, Stringent})\), because all the nonresponders in both regimes are now categorized as failure (ie, both have outcome cell probabilities (0.769, 0.231) and (1,0) for responders and nonresponders, respectively). The comparison between the pair of regimes becomes futile, as valuable information on the intermediate level is now lost. One limitation of the \textit{GOR} is that, the estimates may be biased when at least some of the cell probabilities corresponding to any of the two regimes under comparison are small (say, < 0.05 or so), as discussed in Section 5 of Supplementary Material. However, this phenomenon is not unique to \textit{GOR}, but happens in many classical estimation problems involving categorical data.\textsuperscript{45} Finally, to further expand the scope of the \textit{GOR}, covarites can be considered to analyze the ordinal outcome using proportional odds model based approach. It can be pursued as a future work.
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CONFLICT OF INTEREST STATEMENT

Xiaoxi Yan is one of the founders of Applied Behavior Systems Ltd. Hexis Performance is developed by Applied Behavior Systems Ltd.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy and ethical restrictions.

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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