Received: 8 April 2022 | Accepted: 3 March 2023

DOI: 10.1111/biom.13859

BIOMETRIC METHODOLOGY

Biometrics A JOURNAL OF THE INTERNATIONAL BIOMETRIC SOCIETY WILEY

Longitudinal incremental propensity score interventions for limited resource settings

Aaron L. Sarvet[1] | **Kerollos N. Wanis**[2] | **Jessica G. Young**[2,3] | **Roberto Hernandez-Alejandro**[4] | **Mats J. Stensrud**[1]

[1]Department of Mathematics, École polytechnique fédérale de Lausanne, Lausanne, Switzerland

[2]Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA, USA

[3]Department of Population Medicine, Harvard Pilgrim Health Care Institute, Boston, MA, USA

[4]Division of Transplantation, University of Rochester, Rochester, NY, USA

Correspondence
Aaron L. Sarvet, Department of Mathematics, École polytechnique fédérale de Lausanne, Switzerland.
Email: aaron.sarvet@epfl.ch

Funding information
Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung, Grant/Award Number: 200021_207436

Abstract

Many real-life treatments are of limited supply and cannot be provided to all individuals in the population. For example, patients on the liver transplant waiting list usually cannot be assigned a liver transplant immediately at the time they reach highest priority because a suitable organ is not immediately available. In settings with limited supply, investigators are often interested in the effects of treatment strategies in which a limited proportion of patients receive an organ at a given time, that is, treatment regimes satisfying resource constraints. Here, we describe an estimand that allows us to define causal effects of treatment strategies that satisfy resource constraints: incremental propensity score interventions (IPSIs) for limited resources. IPSIs flexibly constrain time-varying resource utilization through proportional scaling of patients' natural propensities for treatment, thereby preserving existing propensity rank ordering compared to the *status quo*. We derive a simple class of inverse-probability-weighted estimators, and we apply one such estimator to evaluate the effect of restricting or expanding utilization of "increased risk" liver organs to treat patients with end-stage liver disease.

KEYWORDS
causal inference, lifetime and survival analysis, nonparametric methods

1 | INTRODUCTION

When first-line treatments are scarce, patients often face decisions between waiting for a suspected superior treatment or accepting the first available treatment. For example, many patients with end-stage liver disease will reject transplantation with "increased risk" liver grafts (Kumar et al., 2016), which are suspected to confer a higher risk of unintended transmission of HIV, hepatitis B, and/or hepatitis C (Seem et al., 2013). To evaluate the effect of such practices, we could make inferences on parameters of hypothetical randomized trials comparing survival under transplantation with "increased risk" versus "standard risk" liver grafts. Yet, knowledge of these average effect parameters would be insufficient for decisions because it is unclear whether a restrictive policy on "increased risk" organs might adversely and surreptitiously impact overall survival due to longer waiting times. Similar concerns arise

with studies that aim to assess the effects of liberal versus conservative strategies for surgical blood transfusion (Mazer et al., 2017) or of care reception at hospitals with high versus low procedural volume (Vemulapalli et al., 2019).

Observational studies aiming to inform real-world policies should consider treatment strategies compatible with real-world constraints. In limited resource settings, these constraints will primarily include restrictions on treatment utilization in the population. Secondarily, policy decisions concerning the elimination of a suspected inferior treatment will leave unperturbed patients' counterfactual rank ordering in terms of their propensities for treatment, for example, those determined by a transplant waiting list.

A growing literature targets the optimal dynamic treatment regime (DTR) among the restricted class that respects a resource constraint in expectation. However, methods for point treatment settings (Athey & Wager, 2021; Luedtke & van der Laan, 2016) are of limited utility when patients have sequential opportunities for treatment and constraints delay, rather than prevent, treatment. Additionally, more general constrained optimization strategies (e.g., Caniglia et al., 2021) will identify DTRs that contradict extant prioritization strategies (e.g., waiting lists) that a policy-maker wishes to preserve. In contrast, Boatman and Vock (2018) consider estimating the value of regimes for patients who are *offered* organs (lungs) on a transplant waiting list where the structure of the waiting list is left unmanipulated, but suggest intensive simulation-based estimators with unknown statistical properties and require that the waiting list algorithm of the observed data-generating mechanism is precisely known to the analyst. This requirement may be reasonable in transplant settings, where waiting list algorithms are publicly available, but will otherwise not be satisfied, as in the example of care provision at low- versus high-procedural volume care centers.

Motivated by the gaps in the methodological literature, we describe a new class of estimands, which we refer to as expected potential outcomes under *incremental propensity score interventions (IPSIs) for limited resource settings*. IPSIs are characterized by time-varying stochastic interventions on treatment versions that result in proportional shifts in patients' propensities for treatment reception. These interventions are similar to the IPSIs of Kennedy (2019) with the important and nontrivial exception that they are specifically tailored for the time-varying *limited-resource* setting. As in Kennedy (2019), we derive relatively simple inverse-probability-weighted (IPW) estimators for these estimands that are easy to implement with standard statistical software.

We present results of a real data analysis for a setting in which patients are waiting to receive a single dose of one of two treatments versions and policy-makers are considering eliminating the suspected inferior treatment version. In line with the examples above, such settings are common in medicine and public health when patients are faced with decisions between scarce treatments with uncertain wait-times. To fix ideas, we focus on the motivating example of "standard risk" versus "increased risk" liver transplants. However, we emphasize that IPSIs may be formulated to satisfy *any* investigator-specified constraints on the marginal distribution of treatment over time and we provide general results in the Supporting Information. Section 2 presents an observed data structure. Section 3 provides formal definitions of IPSIs and corresponding counterfactual variables. Section 4 provides a numerical example illustrating the utility of IPSIs and the failure of naive methods. Section 5 defines conditions for the identification of expected potential outcomes under IPSIs in terms of observed data parameters and gives identification theorems. Section 6 provides an algorithm for consistent and asymptotically normal estimation of identified parameters. Section 7 provides a real data analysis using data from the Scientific Registry of Transplant Recipients. Section 8 provides concluding remarks. Proofs and additional results are provided in the Supporting Information.

2 | DATA STRUCTURE

Consider a study in which n patients are followed in $k \in \{0, \dots, K\}$ discrete time intervals. Suppose that patients $i \in \{1, \dots, n\}$ represent independent and identically distributed draws from a common law P, and thus, we omit the i subscript on the random variables.

In each interval k, a patient is a candidate for receiving treatment A_k, where $A_{1,k} := I(A_k = 1)$ indicates reception of a *suspected inferior treatment* (e.g., an "increased risk" organ transplant), $A_{2,k} := I(A_k = 2)$ indicates reception of a *suspected superior treatment* (e.g., a "standard risk" organ transplant), and $A_k = 0$ indicates no treatment. Let L_k be a vector of the patient's covariates and let Y_k be an indicator that an event of interest (e.g., death) has occurred by the end of interval k. We define a topological order within each interval as (L_k, A_k, Y_k).

We use overlines (e.g., $\overline{A}_k$) to indicate the history of variables during follow-up through k and underlines (e.g., $\underline{A}_k$) to indicate their future trajectory from (and including) k. By definition, all patients are alive and untreated at baseline, so $A_{-1} = Y_{-1} = 0$ and patients can only receive a single treatment such that if $A_k \in \{1, 2\}$, then $\underline{A}_{k+1} = 0$. For notational convenience, we define the indicator functions $R_{1,k} := I\{Y_{k-1} = \overline{A}_{k-1} = 0\}$ and $R_{2,k} := I\{A_{1,k} = Y_{k-1} = \overline{A}_{k-1} = 0\}$, which indicate eligibility for suspected inferior and superior treatments, respectively. Unless otherwise specified, we let Y_{k-1} be a subset of the covariate vector L_k.

3 | INCREMENTAL PROPENSITY SCORE INTERVENTIONS FOR LIMITED RESOURCE SETTINGS

Here we describe the regimes g, under which the marginal probability of suspected inferior and superior treatments at each time point are constrained to be equal to or less than those probabilities in the observed data. We refer to Web Appendix A for a formulation of regimes g that fix the marginal utilization of treatments to any arbitrary levels.

We use superscripts to denote counterfactual variables under a counterfactual regime. For example, Y_k^g is the counterfactual outcome that would occur under regime g in interval k. Following Richardson and Robins (2013), we use plus symbols (+) to distinguish *natural* values of counterfactual intervention variables under a regime (Robins et al., 2004) (e.g., $A_{1,k}^g$) from *assigned* values of such variables (e.g., $A_{1,k}^{g+}$). Here, we take special care in distinguishing natural and assigned treatment values because they play an integral part in the definition of IPSIs. The natural value of some intervention variable in interval k under some regime g is a random variable corresponding to the treatment value that would occur under that regime had that regime been followed at all intervals prior to, but not through, the moment of intervention on that variable. For example, $A_{1,k}^g$ indicates a patient's inferior treatment status in interval k, had that patient been following regime g through interval $k-1$ but stopped thereafter, and subsequently that treatment is left to arise according to *status-quo* mechanism operating in the factual data. For a thorough introduction to natural treatment values in causal inference, see Richardson and Robins (2013) and also Young et al. (2014). We will denote a patient's eligibility for a specific treatment j under regime g with $R_{j,k}^{g+}$ to emphasize that treatment eligibility is a function of a patient's past *assigned* (as opposed to *natural*) values of treatment (e.g., $R_{1,k}^{g+} := I\{Y_{k-1}^g = \overline{A}_{k-1}^{g+} = 0\}$).

We use the shorthand $\pi_{1,k}^g(a \mid \bar{l}_k)$ to refer to the *natural* probabilities of receiving the suspected inferior treatment level a under regime g among treatment eligible patients with covariate history $\bar{l}_k$: $P(A_{1,k}^g = a \mid R_{1,k}^{g+} = 1, \overline{L}_k^g = \bar{l}_k)$. Likewise, we use $\pi_{1,k}^{g+}(a \mid \bar{l}_k)$ to refer to such *assigned* probabilities of receiving the suspected inferior treatment and $\pi_{1,k}(a \mid \bar{l}_k)$ to such probabilities in the factual data. Similarly, we use $\pi_{2,k}^g(a \mid \bar{l}_k)$, $\pi_{2,k}^{g+}(a \mid \bar{l}_k)$ and $\pi_{2,k}(a \mid \bar{l}_k)$ for suspected superior treatments, except conditioning on $R_{2,k}^{g+} = 1$ (or $R_{2,k} = 1$, for $\pi_{2,k}(a \mid \bar{l}_k)$), that is, conditioning on those not selected for the inferior treatment. Finally, we let $q_k^*(a_k \mid \bar{l}_k, \overline{a}_{k-1})$ denote $P(A_k^{g+} = a_k \mid \overline{L}_k^g = \bar{l}_k, \overline{A}_{k-1}^{g+} = \overline{a}_{k-1})$ and let $q_k(a_k \mid \bar{l}_k, \overline{a}_{k-1})$ denote the analogous probability in the factual data, $P(A_k = a_k \mid \overline{L}_k = \bar{l}_k, \overline{A}_{k-1} = \overline{a}_{k-1})$.

Definition 1 (IPSIs g for limited resource settings). Let $c_{P,1,k}$ and $c_{P,2,k}$ denote investigator-specified parameters defined as some function of P so that, for each k, $c_{P,1,k}$ and $c_{P,2,k}$ are less than or equal to $P(A_{1,k} = 1)$ and $P(A_{2,k} = 1)$, respectively.

Furthermore, let $\gamma_{P,k}^g$ and $\delta_{P,k}^g$ be law-dependent scaling factors defined for each k as:

$$\gamma_{P,k}^g := \frac{c_{P,1,k}}{P(A_{1,k}^g = 1)}, \tag{1}$$

$$\delta_{P,k}^g := \frac{c_{P,2,k}}{P(A_{2,k}^g = 1)}. \tag{2}$$

Then, IPSIs for limited resource settings are defined as the set of stochastic interventions on A_k^{g+} for all k and all $\bar{l}_k$, such that

$$\pi_{1,k}^{g+}(1 \mid \bar{l}_k) = \gamma_{P,k}^g \times \pi_{1,k}^g(1 \mid \bar{l}_k), \tag{3}$$

$$\pi_{2,k}^{g+}(1 \mid \bar{l}_k) = \delta_{P,k}^g \times \pi_{2,k}^g(1 \mid \bar{l}_k). \tag{4}$$

In words, IPSIs are stochastic interventions that proportionally scale treatment-eligible patient's natural propensities for treatments by the scaling factors $\gamma_{P,k}^g$ and $\delta_{P,k}^g$, and are specified by the investigator entirely through selection of the parameters $c_{P,1,k}$ and $c_{P,2,k}$. As we state formally in the following Theorem, $c_{P,1,k}$ and $c_{P,2,k}$ are interpretable as the marginal probabilities of suspected inferior and superior treatment assignment under regime g, so that IPSIs precisely allow control of these counterfactual parameters.

Theorem 1. *For a regime g specified according to Definition 1, then $P(A_{1,k}^{g+} = 1) = c_{P,1,k}$ and $P(A_{2,k}^{g+} = 1) = c_{P,2,k}$ for all k and at all laws P.*

A proof of Theorem 1 is given in Web Appendix B. By consequence of Definition 1, then, for $j \in \{1, 2\}$,

$$q_k^*(j \mid \bar{l}_k, \overline{a}_{k-1}) = \begin{cases} \pi_{j,k}^{g+}(1 \mid \bar{l}_k) & \text{for } r_{j,k} = 1 \\ 0 & \text{for } r_{j,k} = 0. \end{cases} \tag{5}$$

While it is not immediately obvious that $\gamma_{P,k}^g$ and $\delta_{P,k}^g$ will be bounded to the unit interval, we show in Web Appendix A that such is the case, under standard identification conditions introduced in Section 5, so that the intervention densities defined in (5) are guaranteed to be proper probability mass functions.

Note also that $\gamma_{P,k}^g$ and $\delta_{P,k}^g$ are not functions of patient covariates $\overline{L}_k$. An immediate and important consequence

of this property and the boundedness of the scaling factors is the following: for each k, $j \in \{1, 2\}$, the map $\pi^{g+}_{j,k}(1 \mid \cdot)$ can be understood as a transformation of the map $\pi^{g}_{j,k}(1 \mid \cdot)$ that is rank-preserving in the arguments $\bar{l}_k$. In words, the rank orderings of patients' natural propensities are preserved upon intervention under regime g. This is desirable whenever an investigator is interested in a policy that manipulates resource utilization without perturbing the patient prioritization mechanism, whether that mechanism be explicit and known, as in transplantation or emergency department triage, or implicit and/or latent, as in blood transfusion or specialist care prioritization in some settings. In our example, we consider a policy that eliminates "increased risk" liver grafts without perturbing the structure of the liver transplant waiting list.

In summary, the class of IPSI regimes g of Definition 1 is tailored for limited resource settings because they allow specific investigator control of the marginal utilization of treatments, under the regime, to levels at or below those in the observed data. Alternatively, IPSIs can be specified to constrain the marginal resource utilization to any arbitrary level, including levels greater than those in the observed data, which may be of interest in some cases (see the Real Data Analysis in Section 2 for an example). We give flexible definitions of these regimes and generalizations of subsequent identification and estimation results in Web Appendix A. We also show in Web Appendix C that static regimes, under which a particular treatment level is assigned to all patients, correspond to special, and often unrealistic, cases of IPSIs.

In the remainder of the manuscript, we present an illustrative example, and identification and estimation results, for the special case IPSI in which $c_{P,1,k}$ is set to 0 and $c_{P,2,k}$ is set to $P(A_{2,k} = 1)$. In other words, we consider an IPSI in which the suspected inferior treatment is eliminated and utilization of the suspected superior treatment under g is maintained to that in the observed data. By consequence of Theorem 1, we have that $\gamma^{g}_{P,k} = \pi^{g+}_{1,k}(1 \mid \bar{l}_k) = 0$ for all $\bar{l}_k$, and

$$P(A^{g+}_k = 1) = 0, \tag{6}$$

$$P(A^{g+}_k = 2) = P(A_k = 2). \tag{7}$$

We consider this special IPSI to simplify notation and also to anchor presentation in a common query exemplified by our motivating example of a policy to eliminate "increased risk" liver grafts. Furthermore, consideration of this IPSI allows discussion of identification and estimation in this special case, which highlights properties of practical relevance that depart from general results.

4 | ILLUSTRATIVE EXAMPLE

We present a simple numerical example illustrating the failure of naive methods and the utility of IPSIs for satisfying the characteristic constraints of limited resource settings. Consider a population of patients with end-stage liver disease. Suppose that based on previous randomized controlled trials (RCT), it is known that a patient's mortality under transplant with an "increased risk" organ $\mathbb{E}_P[Y_k^{a_k=1}]$ is on average worse than under transplant with a "standard risk" organ, $\mathbb{E}_P[Y_k^{a_k=2}] < \mathbb{E}_P[Y_k^{a_k=1}]$. Further, suppose that policy-makers are interested in evaluating the expected survival under a regime where the use of "increased risk" liver grafts is eliminated, $a_{1,k} = 0$.

Then, consider a setting with $K = 1$, that is, two time points, and suppose that the true parameter values defining the joint distribution of $(\overline{A}_1, \overline{Y}_1)$ are also known. For simplicity, suppose that all patients are alive at the end of the first interval ($\mathbb{E}_P[Y_0] = 0$), but not necessarily thereafter. The marginal probabilities of receiving an "increased risk" organ ($A_{1,k} = 1$) and a "standard risk" organ ($A_{2,k} = 1$) are each 0.2 for $k \in \{0, 1\}$, representing the maximum feasible proportion of the population that could receive each organ type in each interval. Consistent with the hypothetical RCT, the conditional probability of death through interval 1 in the observed data is

$$\mathbb{E}_P[Y_1 \mid A_1 = a_1, A_0 = a_0] = \begin{cases} 0 & \text{for } a_0 = 2, a_1 = 0, \\ 0.5 & \text{for } a_0 = 1, a_1 = 0, \\ 0.25 & \text{for } a_0 = 0, a_1 = 2, \\ 0.75 & \text{for } a_0 = 0, a_1 = 1, \\ 1 & \text{for } a_0 = 0, a_1 = 0, \end{cases} \tag{8}$$

so that, given a particular treatment history, expected survival is always better for "standard risk" organs ($a_k = 2$) than for "increased risk" organs ($a_k = 1$) and receiving any organ ($a_k \in \{1, 2\}$) results in better survival compared to receiving no transplant at all ($a_0 = a_1 = 0$). Marginalizing over the specified distribution of treatment yields $\mathbb{E}_P[Y_1] = 0.5$. Assume that organs were allocated completely at random in the factual data so that the conditional expectations in (8) have the counterfactual interpretation $\mathbb{E}_P[Y_1 \mid A_1 = a_1, A_0 = a_0] = \mathbb{E}_P[Y_1^{a_1,a_0}]$ and also that $\pi^{g}_{j,k} = \pi_{j,k}$. Therefore, for any regime g defined by assigned treatment densities $\pi^{g+}_{1,k}$ and $\pi^{g+}_{2,k}$ for "increased" and "standard risk" organs, the g-formula of Robins (1986) identifies the counterfactual survival under that regime g

$$\mathbb{E}_P[Y_1^g] = \sum_{\overline{A}_1^*} \mathbb{E}_P[Y_1 \mid \overline{A}_1 = \overline{a}_1] \prod_{k=0}^{1} \pi^{g+}_{2,k}(a_{2,k})^{I(r_{2,k}=1)} \pi^{g+}_{1,k}(a_{1,k})^{I(r_{1,k}=1)},$$

where we sum over the five possible treatment histories $\overline{\mathcal{A}}_1^*$.

Suppose that there are two investigators who attempt to provide evidence for the policy decision. Investigator 1 ignores the policy constraint and targets the expected outcome under the static regime g_1 that sets $A_{1,k}^{g_1+} = 0$ for all patients. Computation of the following g-formula identifies $\mathbb{E}_P[Y_1^{g_1}]$, that is,

$$\mathbb{E}_P[Y_1^{g_1}] = \sum_{\overline{\mathcal{A}}_1^*} \mathbb{E}_P[Y_1 \mid \overline{A}_1 = \overline{a}_1] \prod_{k=0}^{1} \pi_{2,k}(a_{2,k})^{I(r_{2,k}=1)} I(a_{1,k} = 0) \approx 0.47.$$

The value of $\mathbb{E}_P[Y_1^{g_1}] \approx 0.47$ suggests that elimination of "increased risk" organs would mark an improvement compared to the regime in the factual data ($\mathbb{E}_P[Y_1] = 0.5$). However, evaluation of other parameters of this regime reveals possible limitations in its policy relevance. In particular, the following g-formulae identify the marginal probabilities of "standard risk" organ utilization under regime g_1,

$$P(A_{2,0}^{g_1} = 1) = \pi_{2,0}(1) = 0.25,$$

$$P(A_{2,1}^{g_1} = 1) = \pi_{2,1}(1)\pi_{2,0}(0) = 0.5 \times 0.75 = 0.375.$$

The marginal utilization of "standard risk" organs under the naive regime g_1 significantly exceeds the constraints in the factual data $P(A_{2,0} = 1) = P(A_{2,1} = 1) = 0.2$, which surely must also be satisfied under any realistic regime.

In contrast, suppose Investigator 2 explicitly considers the policy constraint and evaluates an IPSI regime g_2 that sets $A_{1,k}^{g_2+} = 0$ for all patients and determines $A_{2,k}^{g_2+}$ via the IPSI regime described in Definition 1. Since the intervention densities $\pi_{2,0}^{g_2+}$ and $\pi_{2,1}^{g_2+}$ are not immediately known, Investigator 2 would recursively identify $\pi_{2,k}^{g_2+}$ from $k = 0$ to $k = 1$ with the following series of computations:

0a. $P(A_{2,0}^{g_2} = 1) = \pi_{2,0}(1) = 0.25,$

0b. $\delta_{P,0}^{g_2} = \frac{P(A_{2,0}=1)}{P(A_{2,0}^{g_2}=1)} = 0.8,$

and then,

1a. $P(A_{2,1}^{g_2} = 1) = \pi_{2,1}(1)\pi_{2,0}^{g_2+}(0) = 0.4,$

1b. $\delta_{P,1}^{g_2} = \frac{P(A_{2,1}=1)}{P(A_{2,1}^{g_2}=1)} = 0.5,$

1c. $\pi_{2,1}^{g+}(1) = \delta_{P,0}^{g_2} \times \pi_{2,0}^{g}(1) = 0.25.$

Finally, Investigator 2 would evaluate the g-formula for regime g_2,

$$\mathbb{E}_P[Y_1^{g_2}] = \sum_{\overline{\mathcal{A}}_1^*} \mathbb{E}_P[Y_1 \mid \overline{A}_1 = \overline{a}_1] \prod_{k=0}^{1} \pi_{2,k}^{g+}(a_{2,k})^{I(r_{2,k}=1)} I(a_{1,k} = 0) = 0.65,$$

and would calculate the marginal probabilities of "standard risk" organ utilization under regime g_2,

$$P(A_{2,0}^{g_2+} = 1) = \pi_{2,0}^{g_2+}(1) = 0.2,$$

$$P(A_{2,1}^{g_2+} = 1) = \pi_{2,1}^{g_2+}(1)\pi_{2,0}^{g_2+}(0) = 0.25 \times 0.8 = 0.2.$$

The constraints are satisfied under this regime and importantly, the value of $\mathbb{E}_P[Y_1^{g_2}]$ suggests, in contradiction to Investigator 1, that elimination of "increased risk" organs would mark a *deterioration* in survival compared to the regime in the factual data, that is, $\mathbb{E}_P[Y_1^{g_2}] > \mathbb{E}_P[Y_1] > \mathbb{E}_P[Y_1^{g_1}]$.

We present a visual illustration and numerical summary of treatment assignment for this example in Figure 1. The top third of Figure 1 illustrates treatment utilization under the naive regime g_1, in which the proportion of *eligible* patients who receive the superior treatment version is preserved compared to the observed data. In contrast, the *overall* proportion of patients who receive the superior treatment version is increased due to the increase in the *eligible* patient pool elicited by the elimination of the inferior treatment version. The bottom third of the graph illustrates treatment under the IPSI regime g_2, in which the proportion of *eligible* patients who receive the superior treatment version is reduced compared to the observed data, but the *overall* proportion of such patients is preserved.

In the following Section 5, we present general conditions sufficient to identify expected potential outcomes under an IPSI regime g, $\mathbb{E}_P[Y_k^g]$, from the distributions that generated the observed data described in Section 2. We conclude the section with a theorem that provides an identifying observed data parameter under these conditions.

5 | IDENTIFICATION

We define the model $\mathcal{M}^A$ by the following conditions.

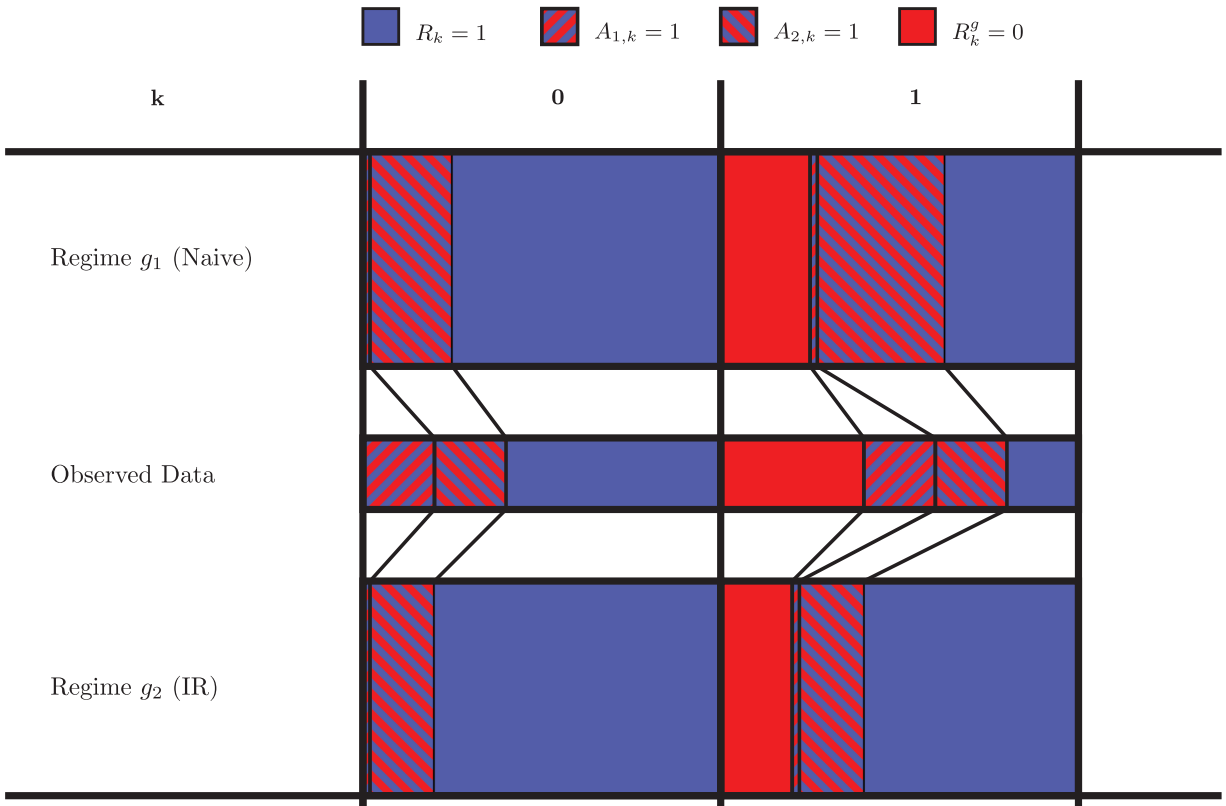
A1a. **Exchangeability 1:**
For each k, $\underline{L}_{k+1}^g \perp\!\!\!\perp A_k^g \mid \overline{L}_k^g, \overline{A}_{k-1}^g$.

A1b. **Exchangeability 2:**
For each k, $\underline{A}_{2,k}^g \perp\!\!\!\perp A_{1,k}^g, A_{2,k-1}^g \mid A_{1,k-1}^g, \overline{L}_{k-1}^g, \overline{A}_{k-2}^g$.

A2. **Consistency** For each k:
if $\overline{A}_k = \overline{A}_k^{g+}$ then $L_{k+1} = L_{k+1}^g$ and $A_{1,k+1} = A_{1,k+1}^g$
and; if $\overline{A}_k = \overline{A}_k^{g+}$ and $\overline{A}_{1,k+1} = \overline{A}_{1,k+1}^{g+}$then $A_{2,k+1} = A_{2,k+1}^g$.

A3. **Positivity** For all
$k, \bar{l}_k, f_{\overline{L}_k^g, R_{1,k}^{g+}=1}(\bar{l}_k) > 0 \Rightarrow f_{A_{1,k}=0, \overline{L}_k, R_{1,k}=1}(\bar{l}_k) > 0.$

Condition **A1a** is equivalent to the "no unmeasured confounding assumption" for future outcomes and covariates



k	0	1
$P(R_{1,k} = 1)$	1	0.6
$\pi_{1,k}(0)$	0.8	$0.\overline{66}$
$\pi_{2,k}(1)$	0.25	0.5
$P(A_{2,k} = 1)$	$1 \times 0.8 \times 0.25 = 0.2$	$0.6 \times 0.\overline{66} \times 0.5 = 0.2$
$P(R_{1,k}^{g_1+} = 1)$	1	0.75
$\pi_{1,k}^{g_1+}(0)$	1	1
$\pi_{2,k}^{g_1}(1)$	0.25	0.5
$P(A_{2,k}^{g_1} = 1)$	$1 \times 1 \times 0.25 = 0.25$	$0.75 \times 1 \times 0.5 = 0.375$
$P(R_{1,k}^{g_2+} = 1)$	1	0.8
$\pi_{1,k}^{g_2+}(0)$	1	1
$\pi_{2,k}^{g_2}(1)$	0.25	0.5
$P(A_{2,k}^{g_2} = 1)$	$1 \times 1 \times 0.25 = 0.25$	$0.8 \times 1 \times 0.5 = 0.4$
$\delta_{P,k}^{g_2}$	$\frac{.2}{0.25} = 0.8$	$\frac{0.2}{0.4} = 0.5$
$\pi_{2,k}^{g_2+}(1)$	$0.8 \times 0.25 = 0.2$	$0.5 \times 0.5 = 0.25$
$P(A_{2,k}^{g_2+} = 1)$	$1 \times 1 \times 0.2 = 0.2$	$0.8 \times 1 \times 0.25 = 0.2$

FIGURE 1 Simple numerical example illustrating the failure of naive methods to respect realistic resource constraints. The width of the striped bars provides geometric intuition for properties of the naive (g_1) and IPSI (g_2) regimes: while the naive regime retains the conditional probability of treatment to that in the observed data, the marginal probability of treatment is unrealistically inflated due to the increased proportion of treatment-eligible patients. In contrast, the IPSI regime shrinks this conditional probability so that the marginal under the regime is alternatively retained.

$\underline{L}_k$ commonly invoked for the identification of parameters under dynamic regimes. We articulate exchangeability conditions in terms of counterfactual variables so that they are amenable to direct interrogation using the Single World Intervention Graphs of Richardson and Robins (2013). When Condition **A1a** is the only exchangeability condition assumed, average treatment effects are generally identified by the g-formula of Robins (1986) even if an investigator fails to measure all common causes of successive treatment $(A_k, A_{k+1}, \dots)$ in the observed data, provided that these treatments under the hypothetical regime were manipulated only as a function of patient's covariate and *assigned* treatment history $(\overline{L}_k^g, \overline{A}_{k-1}^{g+})$ and known parameters. Modified treatment policies (Díaz et al., 2021, 2022; Haneuse & Rotnitzky, 2013)—and regimes (more generally) that assign treatment as a function of the natural treatment value (Richardson & Robins, 2013; Young et al., 2014)—do not fall in this class and Condition **A1a** is not usually sufficient for identification of causal parameters. Although an IPSI regime g does not directly depend on the natural value of treatment, computing the intervention density under g requires knowledge of the marginal distribution of the natural value of the suspected superior treatment $P(A_{2,k}^g = 1)$ as in expression (2) and this counterfactual parameter is not necessarily identified under Condition **A1a** alone. Therefore, we additionally consider Condition **A1b**, which is also implied by the "no unmeasured confounding assumption," for natural superior treatments $\underline{A}_{2,k}^g$, as in Richardson and Robins (2013) and Young et al. (2014). To provide additional intuition for the necessity of **A1b** in this context, note that an unmeasured common cause of some treatment A_k and some V_j (with $j > k$) will typically preclude g-formula identification of the expected value of V_j under some intervention on A_k; this will be as true when $V_j \equiv A_{2,j}$, as it is for the familiar case when $V_j \equiv Y_j$; whereas **A1a** rules out unmeasured common causes of A_k and Y_j, **A1b** is needed to rule out unmeasured common causes of A_k and $A_{2,j}$.

For a regime g considered here, we do not need an analogous exchangeability condition for $\underline{A}_{1,k}^g$ because the intervention distribution for $A_{1,k}^{g+}$ is known a priori, $P(A_{1,k}^{g+} = 1) = 0$. For IPSIs that arbitrarily constrain resources, additional exchangeability conditions for $\underline{A}_{1,k}^g$ may be needed, as outlined in Web Appendix A.

Condition **A2** links observed and counterfactual variables. It states that a patient with observed treatment history consistent with regime g will develop subsequent clinical features and natural treatments consistent with those that would naturally occur under regime g.

Condition **A3** guarantees that the observed data parameter in the forthcoming theorem will be well defined. It states that if a covariate history occurs among treatment-eligible patients with positive probability under regime g, then there must be some positive probability of such patients who do *not* receive the suspected inferior treatment in the observed data. Note that the definition of IPSIs guarantees that an analogous condition for the suspected superior treatment version $(A_{2,k})$ holds; we omit that condition as a model-defining assumption, similar to Kennedy (2019), because its assertion would not exclude any laws $P \in \mathcal{M}^A$. Under arbitrary IPSIs that do not eliminate either treatment, this property would extend to both treatment levels and thus condition **A3** may be omitted entirely (see Web Appendix A).

5.1 | Identification formulae

Let Q_{L_k} denote the density of covariates and outcomes in interval k conditional on the measured past through $k-1$, reminding the reader that $Y_{k-1} \subset L_k$. Then define $f_{V_k}^g(v_k)$ to be a general formulation of a marginal g-formula density of an arbitrary vector $V_k \subseteq \{\overline{A}_k, \overline{L}_k\}$ evaluated at a v_k in the support $\mathcal{V}_k$ of V_k, under regime g

$$f_{V_k}^g(v_k) := \sum_{\{\mathcal{Y}_k, \overline{\mathcal{A}}_k, \overline{\mathcal{L}}_k\} \setminus \mathcal{V}_k} \prod_{j=0}^{k} q_j^*(a_j \mid \bar{l}_j, \bar{a}_{j-1}) Q_{L_j}(l_j \mid \bar{a}_{j-1}, \bar{l}_{j-1}). \quad (9)$$

We leverage this formulation to articulate marginal g-formula densities for various subsets of $\{\overline{A}_k, \overline{L}_k\}$. For example, we write the marginal g-formula density for the outcome Y_{k-1} as in (9), except replacing the terms $(V_k, v_k, \mathcal{V}_k)$ with $(Y_{k-1}, y_{k-1}, \mathcal{Y}_{k-1})$, respectively. As a second example, we write the marginal g-formula density for the *assigned* treatment $A_k = 2$ by replacing $(V_k, v_k, \mathcal{V}_k)$ with $(A_k, 2, \mathcal{A}_k)$. We also define $f_{A'_{2,k}}^g(1)$ to be a marginal g-formula density of $A'_{2,k} = 1$, where $A'_{2,k}$ denotes the unobserved *natural* value of the suspected superior treatment, which takes a different form than $f_{A_k}^g(2)$ because of its inclusion of the factual propensity $\pi_{2,k}$

$$f_{A'_{2,k}}^g(1) := \sum_{\overline{\mathcal{L}}_k} \pi_{2,k}(1 \mid \bar{l}_k) f_{\overline{L}_k, R_{1,k}}^g(\bar{l}_k, 1). \quad (10)$$

In addition, to motivate discrete-time hazards-based estimators, we define for each k the following set of g-formula density hazards $\lambda_k^g \equiv \{\lambda_{Y,k}^g, \lambda_{Y,k}^{g,sub}, \lambda_{A_2,k}^g, \lambda_{A'_2,k}^g\}$. These g-formula density hazards are defined in terms of densities $f_{A'_{2,k}}^g$ and the general densities $f_{V_k}^g$, where V_k is variously instantiated

$$\lambda_{Y,k}^g := \frac{f_{Y_k}^g(1)}{f_{Y_{k-1}}^g(0)}, \quad (11)$$

$$\lambda^{g,sub}_{Y,k} := \frac{f^g_{Y_k,\overline{A}_k}(1,\overline{0})}{f^g_{A_k,Y_{k-1},\overline{A}_{k-1}}(0,0,\overline{0})}, \tag{12}$$

$$\lambda^{g}_{A_2,k} := \frac{f^g_{A_k}(2)}{f^g_{Y_{k-1},\overline{A}_{k-1}}(0,\overline{0})}, \tag{13}$$

$$\lambda^{g}_{A'_2,k} := \frac{f^g_{A'_{2,k}}(1)}{f^g_{Y_{k-1},\overline{A}_{k-1}}(0,\overline{0})}. \tag{14}$$

Then let ψ^g denote the g-formula survival function

$$\psi^g := 1 - \prod_{k=0}^{K}(1 - \lambda^g_{Y,k}). \tag{15}$$

The following Theorem 2 provides a g-formula identity for the expected potential outcomes under the IPSI regime g, $\mathbb{E}_P[Y^g_K]$, following Robins (1986) and Richardson and Robins (2013).

Theorem 2. *Under* $\mathcal{M}^A$, $\mathbb{E}_P[Y^g_K] = \psi^g$.

Theorem 2 by itself does not constitute an identification result for $\mathbb{E}_P[Y^g_K]$ because q^*_j, defined in (5) and appearing in (9), is by definition a counterfactual density. Under classical DTRs, which depend at most on a patient's observed covariates, this distinction is trivial because q^*_j would be known a priori. Under the IPSIs of Kennedy (2019), it is also trivial because q^*_j would be defined directly in terms of the observed propensities $\pi_{2,k}$. In contrast, the intervention densities of the IPSIs of regime g are defined in terms of the parameters $\delta_{P,k}$ and $\pi^g_{2,k}$. Thus, q^*_j is not immediately identified without additional assumptions (i.e., exchangeability condition **A1b**). The following lemma identifies $\pi^{g+}_{2,k}$, which with Theorem 2 suffices to identify $\mathbb{E}_P[Y^g_K]$.

Lemma 1. *Under* $\mathcal{M}^A$, *identify for all* l_0

$$\pi^{g+}_{2,0}(1 \mid l_0) = \frac{P(A_{2,0} = 1)}{\sum_{\mathcal{L}_0} \pi_{2,0}(1 \mid l_0) Q_{L_0}(l_0)} \times \pi_{2,0}(1 \mid l_0).$$

Then, from $k = 1, \ldots, K$, *identify recursively for all* $\bar{l}_k$:

$$\pi^{g+}_{2,k}(1 \mid \bar{l}_k) = \delta^g_{P,k} \times \pi_{2,k}(1 \mid \bar{l}_k),$$

where

$$\delta^g_{P,k} = \frac{P(A_{2,k} = 1)}{\lambda^g_{A'_2,k} \prod_{j=0}^{k-1}(1 - \lambda^{g,sub}_{Y,j})(1 - \lambda^g_{A_2,j})}.$$

Lemma 1 illustrates an unusual feature of IPSIs: the intervention densities q^*_j must be identified (and thus computed) recursively, in terms of observed data parameters, from the first interval to the last. In contrast, intervention densities for Kennedy (2019) are simultaneously identified across all time points.

We give a proof of Theorem 2 and Lemma 1 in the more general case where treatment resources are arbitrarily constrained in Web Appendix D.

5.1.1 | Alternative representations of the g-formula

Define W^g_k to be a random variable that is the product of the ratios of a patient's conditional likelihoods of treatment under the counterfactual regime to that likelihood under the factual regime,

$$W^g_k := \prod_{j=0}^{k} \frac{q^*_j(A_j \mid \overline{L}_j, \overline{A}_{j-1})}{q_j(A_j \mid \overline{L}_j, \overline{A}_{j-1})}. \tag{16}$$

Then, Lemma 2 provides a representation of Theorem 2 that naturally motivates a class of IPW estimators easily computed with off-the-shelf software.

Lemma 2. *Under* $\mathcal{M}^A$, $\pi^{g+}_{2,0}(1 \mid l_0)$ *can be reformulated as*

$$\pi^{g+}_{2,0}(1 \mid l_0) = \frac{P(A_{2,0} = 1)}{\mathbb{E}_P[\frac{A_{2,0}}{\pi_{1,0}(0|L_0)}]} \times \pi_{2,0}(1 \mid l_0),$$

and for each k, $f^g_{V_k}(v_k)$ *and* $f^g_{A'_{2,k}}(1)$ *can be reformulated as*

$$f^g_{V_k}(v_k) = \mathbb{E}_P\left[I(V_k = v_k) W^g_k\right],$$

$$f^g_{A'_{2,k}}(1) = \mathbb{E}_P\left[\frac{A_{2,k} W^g_{k-1}}{\pi_{1,k}(0 \mid \overline{L}_k)}\right].$$

Lemma 2 allows recursive construction of ψ^g entirely in terms of weighted expectations of observed survival and treatments.

6 | INVERSE PROBABILITY WEIGHTED ESTIMATION OF RISK UNDER INCREMENTAL PROPENSITY SCORE INTERVENTIONS

In low-dimensional settings, we can estimate $\mathbb{E}[Y^g_K]$ nonparametrically by estimating each component of the g-formula in Theorem 2, or equivalently, each component of the alternative formulation in Lemma 2. In high-dimensional settings, for example, when L_k takes

many levels and/or when K is large, the g-formula in Theorem 2 may be amenable to nonparametric estimation using machine learning methods via approaches based on the efficient influence function (EIF)—see, for example, Bickel et al. (1993) and Van Der Laan and Rubin (2006). Study of the EIF and resulting EIF-based estimators are the focus of ongoing work but are complicated by the recursive construction of the statistical functional, as illustrated in Lemma 1. Alternatively, in such settings, the nonparametric identification assumptions in Section 5 may be supplemented by parametric modeling assumptions on the propensities $\pi_{1,k}$ and $\pi_{2,k}$, which motivate simple inverse propensity-weighted estimators.

6.1 | Inverse probability-weighted estimation

Let $\widehat{\psi}^g$ be the solution to the estimating equation

$$\sum_{i=1}^{n} U(\psi^g, \widehat{\eta}) = 0, \tag{17}$$

with respect to ψ^g where $U(\psi^g, \widehat{\eta}) := (Y_K - \psi^g) W^g_{K,\widehat{\eta}}$.

Here, $W^g_{k,\widehat{\eta}}$ is defined as in Lemma 2, except with the functions q_j and q_j^* defined in terms of the estimated propensities $\pi_{1,k}(\widehat{\eta}_1)$ and $\pi_{2,k}(\widehat{\eta}_2)$ instead of $\pi_{1,k}$ and $\pi_{2,k}$, where $\boldsymbol{\eta} \equiv \{\eta_1, \eta_2\}$; $\pi_{1,k}(\eta_1)$ and $\pi_{2,k}(\eta_2)$ are parametric models for $\pi_{1,k}$ and $\pi_{2,k}$; and $\widehat{\eta}_1$ and $\widehat{\eta}_2$ are the MLEs of η_1 and η_2.

Following standard m-estimation theory (Stefanski & Boos, 2002), a consistent and asymptotically normal solution for $\widehat{\psi}^g$ may be obtained by recursively obtaining and substituting $(\delta^{g_1}_{\widehat{\eta},k}, W^g_{k,\widehat{\eta}}, \widehat{\lambda}^g_k)$ for $(\delta^{g_1}_{P,k}, W^g_k, \lambda^g_k)$ from $k = 0, \ldots, K$, provided that we choose some $\sqrt{n}$-consistent estimator for the propensities $\pi_{1,k}$ and $\pi_{2,k}$. Note that $(\delta^{g_1}_{\widehat{\eta},k}, W^g_{k,\widehat{\eta}})$ are distinguished from $(\delta^{g_1}_{P,k}, W^g_k)$ via indexing by $\widehat{\eta}$.

We illustrate with the following estimation algorithm, applied to a subject-interval dataset, constructed such that each subject will have $K^* + 1$ lines indexed by $k = 0, \ldots, K^*$, where $K^* = K$ if $Y_K = 0$, else $K^* = \min\{j : Y_j = 1\}$, so that $K^* = K$ when a subject is alive at the end of follow-up or equals the interval number during which a subject dies during follow-up. Let $\mathbb{P}_n$ denote the empirical measure.

6.1.1 | IPW estimation algorithm for ψ^g

1. Using subject interval records with $R_{j,k} = 1$, obtain $\sqrt{n}$-consistent estimates $\pi_{j,k}(\widehat{\eta}_1)$ of $\pi_{j,k}$ for $j = 1, 2$.
2. Obtain

$$\delta^g_{\widehat{\eta},0} = \frac{\mathbb{P}_n(A_{2,0})}{\mathbb{P}_n\left(A_{2,0}\frac{I(A_{1,0}=0)}{\pi_{1,0}(0|L_0;\widehat{\eta}_1)}\right)}.$$

   Then determine $q_0^*(A_0 \mid L_0; \widehat{\boldsymbol{\eta}})$ as in expressions (3)–(5), except using $\delta^g_{\widehat{\eta},0}$ and $\pi_{2,0}(\widehat{\boldsymbol{\eta}})$ in place of $\delta^g_{P,0}$ and $\pi^g_{2,0}$.
3. For each subject's line 1, attach the weight, $W^g_{0,\widehat{\eta}}$, calculated as $\frac{q_0^*(A_0|L_0;\widehat{\eta})}{q_0(A_0|L_0;\widehat{\eta})}$.
4. Compute $\widehat{\lambda}^g_{A_2,0} = \frac{\mathbb{P}_n(A_{2,0}W^g_{0,\widehat{\eta}})}{\mathbb{P}_n(W^g_{0,\widehat{\eta}})}$, $\widehat{\lambda}^g_{Y,0} = \frac{\mathbb{P}_n(Y_0 W^g_{0,\widehat{\eta}})}{\mathbb{P}_n(W^g_{0,\widehat{\eta}})}$, and $\widehat{\lambda}^{g,sub}_{Y,0} = \frac{\mathbb{P}_n(Y_0(1-A_{2,0})W^g_{0,\widehat{\eta}})}{\mathbb{P}_n((1-A_{2,0})W^g_{0,\widehat{\eta}})}$.
5. Iterate from $k = 1, \ldots K$:
   5.1. Obtain $\widehat{\lambda}^g_{A'_2,k} = \frac{\mathbb{P}_n\left(A_{2,k}W^g_{k-1,\widehat{\eta}}\frac{I(A_{1,k}=0)}{\pi_{1,k}(0|\overline{L}_k;\widehat{\eta}_1)}\right)}{\mathbb{P}_n\left(R_{1,k}W^g_{k-1,\widehat{\eta}}\frac{I(A_{1,k}=0)}{\pi_{1,k}(0|\overline{L}_k;\widehat{\eta}_1)}\right)}$.
   5.2. Obtain $\delta^g_{\widehat{\eta},k} = \frac{\mathbb{P}_n(A_{2,k})}{\widehat{\lambda}^g_{A'_2,k}\prod_{j=0}^{k-1}(1-\widehat{\lambda}^{g,sub}_{Y,j})(1-\widehat{\lambda}^g_{A_2,j})}$ and determine $q_k^*(A_k \mid \overline{L}_k; \widehat{\boldsymbol{\eta}})$ as in step 2.
   5.3. For each subject's line k, attach the weight, $W^g_{k,\widehat{\eta}}$, calculated as $\frac{q_k^*(A_k|\overline{L}_k;\widehat{\eta})}{q_k(A_k|\overline{L}_k;\widehat{\eta}))}$.
   5.4 Obtain $\widehat{\lambda}^g_{A_2,k} = \frac{\mathbb{P}_n(A_{2,k}W^g_{k,\widehat{\eta}})}{\mathbb{P}_n(R_{1,k}W^g_{k,\widehat{\eta}})}$, $\widehat{\lambda}^g_{Y,k} = \frac{\mathbb{P}_n(Y_k(1-Y_{k-1})W^g_{k,\widehat{\eta}})}{\mathbb{P}_n((1-Y_{k-1})W^g_{k,\widehat{\eta}})}$ and $\widehat{\lambda}^{g,sub}_{Y,k} = \frac{\mathbb{P}_n(Y_k(1-A_{2,k})R_{1,k}W^g_{0,\widehat{\eta}})}{\mathbb{P}_n((1-A_{2,k})R_{1,k}W^g_{0,\widehat{\eta}})}$.
6. Obtain $\widehat{\psi}^g = 1 - \prod_{k=0}^{K}(1 - \widehat{\lambda}^g_{Y,k})$.

Because the statistical parameter in Theorem 2 is a function of the propensities, unlike most g-formula parameters, any variance estimator that does not explicitly account for the variance in the propensity estimates (e.g., the commonly used sandwich estimator) may be anticonservative. See Haneuse and Rotnitzky (2013) and Henmi and Eguchi (2004) for further discussion. In practice, we recommend the nonparametric bootstrap for variance estimation, which we implement for the applied example in Section 7.

7 | REAL DATA ANALYSIS

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the United States submitted by the members of the Organ Procurement and Transplantation Network

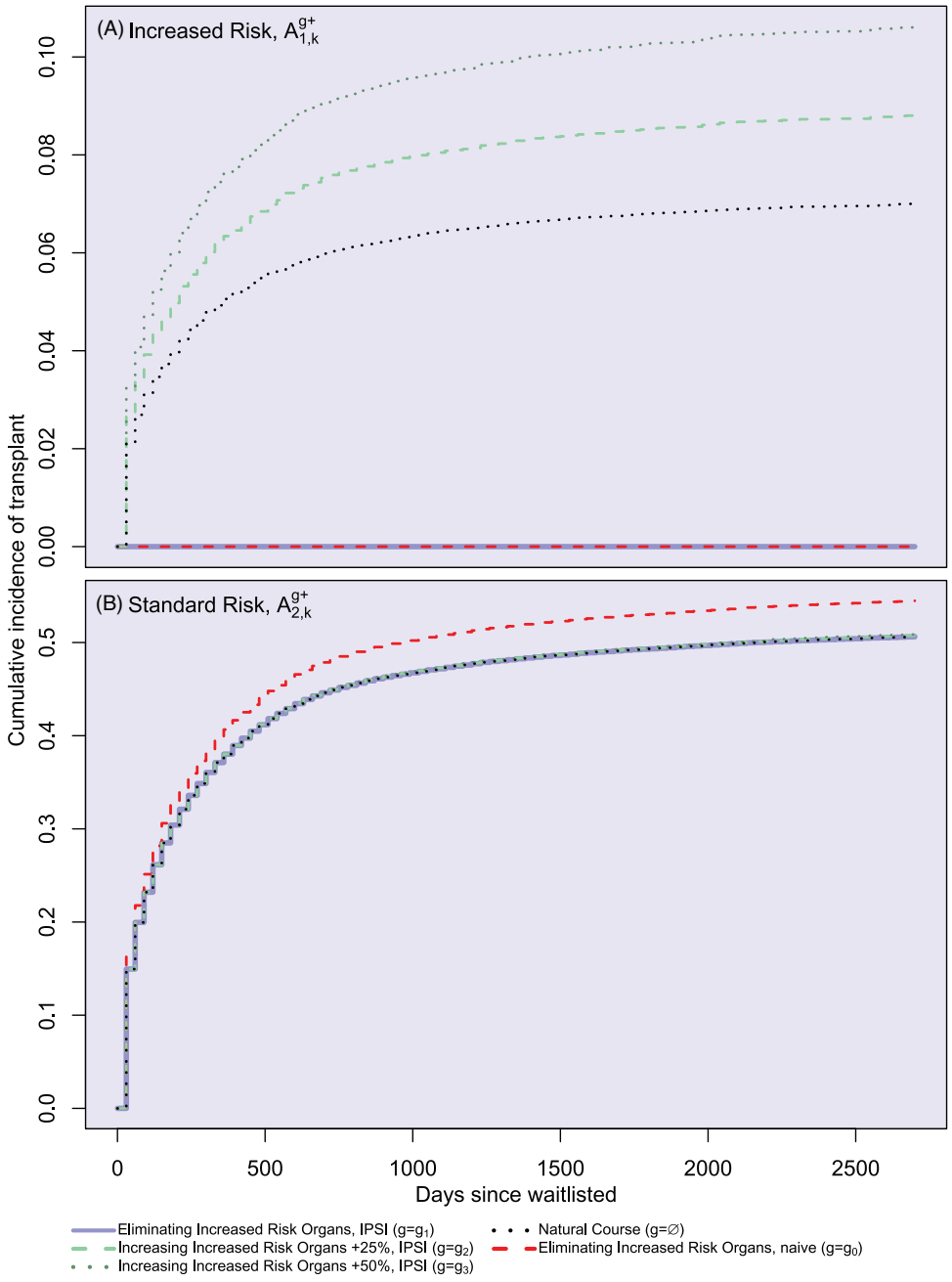


FIGURE 2 Estimated cumulative utilization of treatment. IPSIs constrained "standard risk" organ utilization to natural levels, in contrast to the naive regime. "Increased risk" organ utilization is increased as expected under IPSI regimes g_2 and g_3.

(OPTN). The Health Resources and Services Administration, US Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. We used SRTR data to study the causal effect of different transplantation policies involving the utilization of "increased risk" liver grafts on patient survival. The data were restricted to those from patients aged 18 or older with no prior history of liver transplantation, who were eligible for liver transplantation, were added to the OPTN waiting list to receive a liver organ between 2005 and 2015, and were followed until death, loss to follow-up (as reported by individual transplant programs), or May 31st, 2016, whichever occurs first. The SRTR includes data on wait-list candidate mortality via linkage to the National Death Index (Kim et al., 2019). Over the study period, $n =$ 93,956 transplant candidates were added to the wait list, of whom 45,454 received livers from deceased donors. Data were coarsened into discrete 30-day intervals, where $k = 0$ corresponds to a patient's first 30-day interval upon entering the wait list. Data were used to estimate the 7.5-year cumulative incidence of death ($\mathbb{E}_P[Y_K^{g_z}]$ where $K + 1 = 90$) under the following regimes:

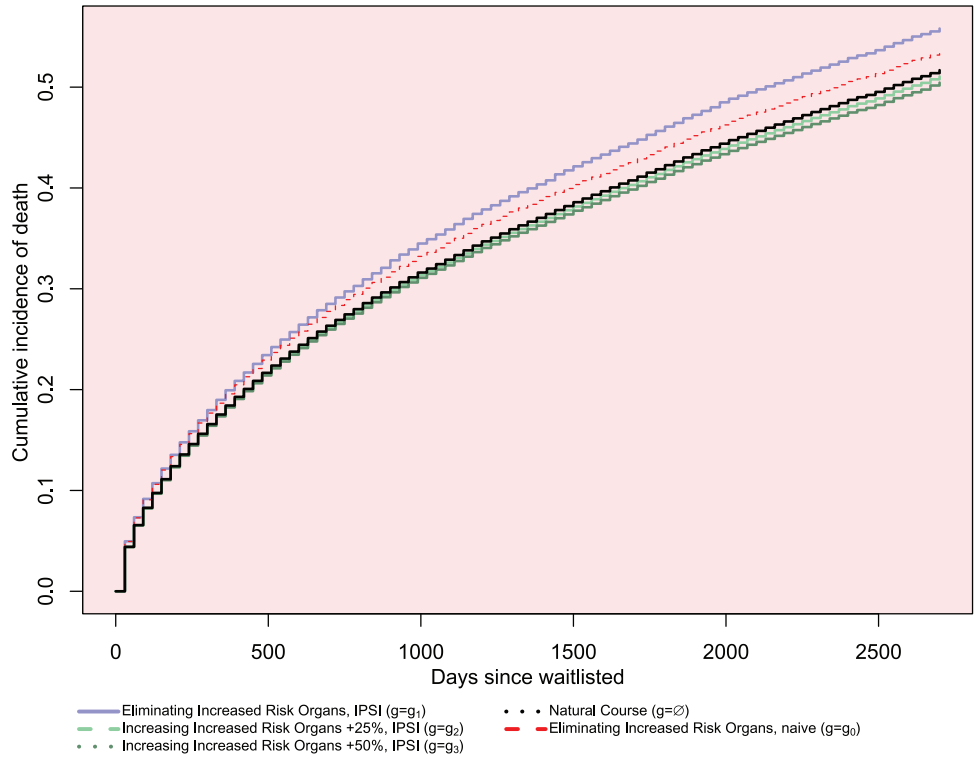


FIGURE 3 Estimated cumulative incidence of death. The naive method under-estimates cumulative incidence of death compared to an IPSI. IPSIs that increase "increased risk" organ utilization indicate lower incidence of death compared to the natural course.

- $\emptyset$. Natural course: "standard risk" and "increased risk" organs are utilized at current levels,
- g_0. Eliminating "increased risk" organs (naive),
- g_1. Eliminating "increased risk" organs (IPSI),
- g_2. Increasing "increased risk" organs +25% (IPSI),
- g_3. Increasing "increased risk" organs +50% (IPSI),

where each of these regimes targets outcomes additionally under hypothetical interventions that abolish censoring and, for simplicity, under interventions that abolish utilization of transplants other than "standard risk" or "increased risk" organs (organs from living donors, cardiac-death donors, donors who are not HIV, hepatitis C, and hepatitis B seronegative, or donors with unknown risk status). Each IPSI ($g_1 - g_3$) constrains "standard risk" organs to the marginal utilization under the natural course. Note that the regimes g_2 and g_3 are examples of general IPSIs described in the Web Appendix A. We consider the naive regime g_0 to be that which eliminates "increased risk" organs and implicitly allows eligible patients under the regime to receive transplants with "standard risk" organs with the same propensity that they would under the natural course (as in the example of Section 4).

We defined $A_{1,k}$ to indicate reception of an "increased risk" organ and $A_{2,k}$ to indicate reception of a "standard risk" organ in interval k. For $k = 0, \ldots, K$, interval k confounders L_k included waiting-list priority in the form of model for end-stage liver disease (MELD) score, MELD score exception, and urgent-need status. Interval 0 confounders L_0 additionally included year of listing to the waiting list, gender, race, age, height, weight, willingness to accept a less optimal organ (i.e., a liver segment, an organ from an incompatible blood type donor, or a donor with hepatitis B or C), need for life support, functional status, primary diagnosis leading to liver failure, history of complications, or procedures related to liver failure (i.e., spontaneous bacterial peritonitis, portal vein thrombosis, transjugular intrahepatic portosystemic shunt). We specify the propensity models in Web Appendix E.

7.1 | Results

We visually confirm that the treatment resource constraints are satisfied under IPSIs by plotting the estimated utilization of "standard risk" and "increased risk" organs under the IPSIs over a follow-up period of 7.5 years in Figure 2. Notably, estimated utilization of "standard risk" grafts under the naive regime is markedly, and unrealistically, elevated compared to the natural course.

The estimated 7.5-year cumulative incidence of death is 51.7% (95% confidence interval [CI]: 51.2–52.2%) under the natural course regime, in contrast to 55.8% (95% CI: 55.3–56.4%) under regime g_1, corresponding to the

restrictive practice of using only "standard risk" organs, an estimated difference of 4.1 percentage points (95% CI: 3.7–4.5 percentage points). Under the naive regime (g_0), the estimated 7.5-year cumulative incidence of death is 53.5% (95% CI: 53.0–54.0%). While the naive regime similarly identifies that the elimination of "increased risk" organs has a detrimental effect on long-term survival, its estimates are optimistic compared to the IPSI that constrains "standard risk" organ utilization to natural levels. The cumulative incidence curves for death under the natural course and regimes g_0 and g_1 are displayed in Figure 3.

The estimated 7.5-year cumulative incidence of death is 51.1% (95% CI: 50.6–51.6%) under regime g_2, corresponding to the expansive practice of increasing utilization of "increased risk" organs by 25%, an incidence 0.6 percentage points lower than what would be observed under the natural course (95% CI: −0.7 to −0.4 percentage points). The estimated cumulative incidence is 50.5% (95% CI: 49.9–51.0%) under regime g_3, corresponding to the expansive practice of increasing utilization of "increased risk" organs by by 50%. That is, an incidence 1.2 percentage points lower than what would be observed under regime g_0 (95% CI: −1.5% to −0.9% percentage points). The cumulative incidence for death under regimes g_2 and g_3 is also displayed in Figure 3.

In summary, we estimated that, despite the concerns regarding infectious disease transmission and organ inferiority, a policy of abolishing utilization of "increased risk" organs would have increased the cumulative incidence of death at 7.5 years and that increasing utilization of "increased risk" organs would actually increase overall survival compared to current practice.

Ninety-five percent confidence intervals were obtained from the 2.5th and 97.5th percentiles of the distribution of point estimates obtained by repeating the IPW algorithm on 500 nonparametric bootstrap samples.

8 | CONCLUSION

We have presented a new class of estimands that satisfy user-specified resource constraints in longitudinal settings with complex confounding structures: expected potential outcomes under *IPSIs* for limited resource settings. These estimands have desirable features compared to traditional estimands because they (i) incorporate substantive knowledge to specify limits on treatment utilization that are feasibly achieved under an actual policy and (ii) coarsely preserve features of the observed joint distribution between treatment and covariates, that is, the patients' relative ordering with respect to their treatment propensities, which would naturally be unperturbed in settings where the intervention is a manipulation of treatment resource scarcity.

Our estimands stand in contrast to the classical average treatment effect of a deterministic regime, which is a special case of an IPSI where treatment resources are assumed to be practically unlimited. We give simple IPW estimators for IPSIs, which can be implemented with off-the-shelf software. These estimators are consistent under mildly stronger exchangeability assumptions, which are usually required for regimes that depend on the natural value of treatment (Young et al., 2014), but also mildly weaker positivity assumptions, like in Kennedy (2019), than those typically needed for most causal estimands.

We demonstrated the utility of IPSIs in a study of organ transplantation policies, where treatment resource limitations are severe. This analysis supports the continued, and possible expanded, use of the suspected inferior treatment resource (the so-called "increased risk" liver grafts), suggesting that the increased scarcity imposed by elimination of these grafts outweighs the suspected inferiority of receiving these grafts, with respect to the cumulative incidence of death in the population of transplant eligible patients.

Our class of estimands generalizes previously used unlimited resource estimands. However, as discussed in Kennedy (2019), these estimands should be interpreted as more descriptive rather than prescriptive, because future interventions will not be implemented exactly as the IPSIs are defined. Further, policy-makers might be interested in effects of different treatment prioritization rules, for example, new (hypothetical) allocation policies corresponding to new algorithms for prioritizing (ranking) individuals on the national waiting list for liver transplants. Such estimands fall outside of the class defined by IPSIs, because such estimands cannot be defined under interventions that preserve the natural prioritization of patients with different covariate values, which is the *incremental* nature of IPSIs. New methods that allow for a wider range of allocation policies are the focus of future work.

ACKNOWLEDGMENTS

The data reported here have been supplied by the Hennepin Healthcare Research Institute (HHRI) as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government. We also thank Lan Wen, James Robins, Thomas Richardson, and Elizabeth Ogburn for insightful comments and discussions.

DATA AVAILABILITY STATEMENT

The data used in this paper are available from Scientific Registry of Transplant Recipients (https://www.srtr.org/)

by request. The codes and scripts for data preprocessing and reproducing all results in this paper are available at GitHub (2023) (https://github.com/AaronSarvet/IPSI-Biometrics).

ORCID

Aaron L. Sarvet https://orcid.org/0000-0002-7621-8570
Mats J. Stensrud https://orcid.org/0000-0001-9641-1936

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SUPPORTING INFORMATION

Web Appendices referenced in Sections 3, 5, and 7 are available at the Biometrics website on Wiley Online Library.

How to cite this article: Sarvet, A.L., Wanis, K.N., Young, J.G., Hernandez-Alejandro, R. & Stensrud, M.J. (2023) Longitudinal incremental propensity score interventions for limited resource settings. *Biometrics*, 1–13. https://doi.org/10.1111/biom.13859