Analysis of “Learn-As-You-Go” (LAGO) Studies

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Abstract

In learn-as-you-go (LAGO) adaptive designs, the intervention is a package consisting of multiple components, and is adapted in stages during the study based on past outcomes. This formalizes standard practice, and desires for practice, in public health intervention studies. Typically, an effective intervention package is sought, while minimizing cost. The main complication when analyzing data from a learn-as-you-go design is that interventions in later stages depend upon the outcomes in the previous stages. Therefore, conditioning on the interventions would lead to effectively conditioning on the earlier stages’ outcomes, which violates common statistical principles. We develop a method to estimate intervention effects from a learn-as-you-go study. We prove consistency and asymptotic normality using a novel coupling argument, and ensure the validity of the test for the hypothesis of no overall intervention effect. We further develop a confidence set for the optimal intervention package and confidence bands for the success probabilities under different package compositions. We illustrate our methods by applying them to the BetterBirth Study, which aimed to improve maternal and neonatal outcomes in India.

1 Introduction

Adaptive designs are popular in clinical trials and other studies, and have been investigated for decades. A typical goal of an adaptive design is to allow researchers to modify or stop a study to improve the chances of reaching firm conclusions with improved efficiency, without jeopardizing the legitimacy and the soundness of the trial (FDA, 2016).

The existing literature on adaptive designs has thus far considered several types of design modifications, including blinded sample size reassessment, group sequential
testing, interim analysis for benefit or futility, successive re-randomizations, changing subgroup proportions or eligibility criteria of the trial (Rosenblum and van der Laan, 2011), and dropping treatment arms. Among the techniques implemented to preserve the validity of statistical inference when analyzing data that was subject to design adaption, the conditional error function (Proschan and Hunsberger, 1995; Müller and Schäfer, 2001, 2004) has been proposed for the design adjustment, and combination functions have been used to aggregate $p$-values from multiple stages (Bauer and Kohne, 1994; Brannath et al., 2002). See Bauer et al. (2016) for a recent comprehensive review of adaptive designs in clinical trials. In addition to valid testing, methods have been developed for estimation in an adaptive group sequential design (e.g. Gao et al., 2013).

Our work is motivated by large-scale public health intervention studies of complex multi component intervention package. In these newly proposed “learn-as-you-go” (LAGO) designs, the intervention, which can e.g. be a treatment, a device, or a new way to organize care, is composed of several components. While subject matter experts have some knowledge with regards to the preferred intervention package, its optimal development is an inherent part of the study goals. A LAGO study is conducted in stages. After each stage, the data collected so far are analyzed, the intervention package is reassessed, and a revised intervention package is put to use in the next stage. The main complication with the LAGO design, compared to standard designs, is that the composition of the intervention package in later stages depends on previous-stage trial results.

The Sequential Multiple Assignment Randomized Trial (SMART) design (Murphy, 2005; Murphy et al., 2007) is a design which randomizes each of the participants at more than one time point, with randomization options and probabilities that depend on past characteristics (and outcomes) of the same patient. Patients are randomized to pre-specified treatment algorithms to determine which of the pre-specified algorithms should be used in practice. The aim of a SMART trial is to find the optimal dynamic treatment regime for each patient, that is, the optimal sequence of treatments, each dependent on patient’s current characteristics. LAGO, however, is aimed at finding an optimal intervention package that is not dynamic. The multi phase optimization strategy (MOST, Collins et al., 2014) consists of three phases: preparation, optimization and evaluation. The development of the optimal intervention package is part of the optimization, while another trial is carried out in the evaluation phase to compare the optimized intervention package to a control group and test for statistical difference between the two groups. The aim of MOST is similar to LAGO; to develop an optimal intervention package and estimate its impact, but the approach is different.

At face value, one may consider phase I dose-finding studies as similar to the problem of adapting the intervention package. In dose-finding studies, the goal is to find the maximum tolerated dose, which is the highest dose of a drug such that adverse effects of the drug are under control. Dose values are assigned to patients in a sequential manner, and in each step a decision is made to stop and declare the maximum tolerated dose or to continue, and if so, with which dose. The more traditionally used methods include the “3 + 3” and “accelerated titration” designs (Simon et al., 1997; Wong et al., 2016). Another popular method is the continual reassessment method (O’Quigley et al., 1990; O’Quigley and Shen, 1996), which assigns each patient the current estimated maximum
tolerated dose. Methods were also developed for the optimal dose of two drugs simultaneously (Thall et al., 2003; Wang and Ivanova, 2005). Rosenberger and Haines (2002) provide a review of the continual reassessment method and additional statistical methods for dose finding studies. Dose-finding studies generally have too small sample sizes to address asymptotic properties of estimators. In public health intervention studies, as opposed to dose-finding studies, the magnitude of the per-stage sample size is typically much larger than the sample size in dose-finding studies, and the number of stages is limited. Additionally, unlike dose-finding studies, where methods are considered for a single or at most dual treatments, interventions in LAGO studies can be composed of multiple components, typically some of them continuous.

An ad hoc example of a precursor to a formal LAGO study is the “BetterBirth Study” (Hirschhorn et al., 2015; Semrau et al., 2017) by Ariadne Labs, a joint center between Brigham and Women’s Hospital and the Harvard T.H. Chan School of Public Health. The BetterBirth Study assessed the use of a 31-item checklist of best practices during labor and delivery that are feasible in resource-limited settings, in order to reduce mortality of mothers and newborns around birth. The intervention was adapted and tested in a three phase process in Uttar Pradesh, India. The goal of the study was to reduce neonatal and maternal mortality rates, which are very high in Uttar Pradesh, with neonatal mortality of 32 per 1000 live births and maternal mortality of 258 per 100,000 births (Semrau et al., 2017). During the first two phases, the intervention was adapted, and a final version was tested in a cluster randomized trial. The BetterBirth Study, funded by a $14.1 million grant from the Bill and Melinda Gates Foundation, included 157,689 mothers and newborns.

The first goal of a LAGO study is to identify the optimal intervention package such that the cost of the intervention is minimized and the probability of a desired binary outcome is above a given threshold. For example, in the BetterBirth Study, the outcome could be the use of the World Health Organization’s (WHO) Safe ChildBirth checklist, with the aim being, for example, that the checklist is used during at least 90% of the births. In the illustrative example included in this paper, we investigate a process outcome, oxytocin administration after delivery, with the aim being that 85% of mothers will receive oxytocin after delivery, as recommended by the WHO, as a proven intervention for preventing postpartum hemorrhage. It is of interest to investigate whether the use of a multiple component intervention package that includes on-site coaching visits and an intervention launch, increases the oxytocin administration, compared to standard of care.

The analysis of a LAGO study is complicated by the fact that the data are not an independent sample. Beginning with the second stage, the recommended intervention package is itself a random variable that depends on previous outcomes. Therefore, conditioning on the interventions would lead to effectively conditioning on the earlier-stage outcomes, which violates standard statistical principles. LAGO studies, however, use the data combined from all stages in the final analysis. When considering the asymptotic behavior of the estimators, we assume that the sample size in each stage increases at a similar rate. In addition, we assume that the next stage intervention converges in probability to a constant as the number of observations in the first stages goes to infinity. This would happen, under the usual regularity conditions, if the next stage intervention
We propose estimators under a LAGO study allowing for several stages, multiple centers or sites, multiple component interventions, center-specific baseline covariates that influence the outcome rate, or center-specific deviations from the recommended intervention, or both. We show that even in this complicated setup, the optimal intervention can be learned from the combined data from all stages. We prove consistency and asymptotic normality of the new estimators utilizing a novel coupling argument. We further establish the validity of tests for an overall intervention framework effect. Finally, we develop a confidence set for the optimal intervention package and confidence bands for the outcome probabilities under various observed or hypothesized intervention packages.

2 The learn-as-you-go design, estimation and theory

In the following section, we present the LAGO design and suggest estimators for individual component effects and the optimal intervention package. Then, we cover asymptotic theory and inference using the asymptotic distribution.

2.1 Description of the learn-as-you-go design

The methods we develop in this paper are for an arbitrary number of stages \( K \). For clear presentation, we focus on a LAGO study consisting of two stages, and extend the methods and theory to studies with more than two stages in Section 3 of the supplementary materials. At each stage \( k \), a version of the intervention package is implemented in each of \( J_k \) centers. Let \( n_{jk} \) denote the sample size (e.g. the number of births) in the \( j \)-th center at stage \( k \). We assume that each center is included in one stage only. In a randomized controlled trial, centers may be randomized to either intervention or control. Alternatively, data might be collected pre and post the implementation of the intervention package and then a center contributes data to both the intervention and the control. Alternatively, data might be collected pre and post the implementation of the intervention package and then a center contributes data to both the intervention and the control.

When we develop asymptotic theory, we consider the situation where the number of patients per center goes to infinity at the same rate in both stages. This will lead to reliable approximations if the number patients in each center is relatively large. Let \( n_k = \sum_{j=1}^{J_k} n_{jk} \) be the number of patients in stage \( k \) and \( n = \sum_{k=1}^{K} n_k \) be the total number of patients. To allow for asymptotic inference, we assume that the ratio between the number of patients in each center and the total sample size \( n \) converges to a constant, and write \( \alpha_{jk} = \lim_{n \to \infty} n_{jk}/n \); then, \( \sum_{k=1}^{K} \sum_{j=1}^{J_k} \alpha_{jk} = 1 \). Define \( \bar{n}_k = (n_1, \ldots, n_k) \).

The multivariate intervention package is composed of \( p \) components. Let \( \mathcal{X} \) be the support of the intervention, that is, all possible intervention values. For example, if all \( p \) intervention components are continuous and each is constrained to be within a given interval \( [L_r, U_r], r = 1, \ldots, p \), then \( \mathcal{X} = [L_1, U_1] \times [L_2, U_2] \times \cdots \times [L_p, U_p] \). Throughout this paper, we assume that \( \mathcal{X} \) is bounded.

We make a distinction between the \textit{recommended} intervention and the \textit{actual} intervention. Typically, the recommended intervention in stage \( k \) is the estimated optimal intervention given prior collected data, \( \hat{x}_{\text{opt.}(k,\bar{n}_{k-1})} \), and can be center specific,
\( \tilde{x}_{j}^{\text{opt.}(k,n_{k-1})} \), for center \( j \). For stage 1, an initial \( x^{(1)} \) or \( x_{j}^{(1)} \) is chosen by researchers, based on subject matter assessments. In large scale public health settings, the actual intervention, denoted by \( A \), may differ from the recommended intervention, due to local constraints or preferences. We denote \( z \) for center-specific characteristics reflecting baseline heterogeneity between centers with respect to the outcome of interest and we consider them fixed, i.e., they are not part of the intervention package. For each center, \( z \) could be, for example, the district of the health center or its monthly birth volume.

We assume that the probability of success for a single unit (e.g., person or birth) in a center with characteristics \( z \) under intervention \( A = a \), \( p_{a}(\beta; z) = p_{r}(Y = 1 \mid A = a, X = x, z; \beta) \), does not depend on the recommended intervention \( x \), except through the actual intervention \( a \), and follows a logistic regression model

\[
\logit p_{a}(\beta; z) = \beta_{0} + \beta_{T}^T a + \beta_{z}^T z, \tag{1}
\]

where \( \beta^T = (\beta_{0}, \beta_{T_{1}}, \beta_{z}) \) is a vector of unknown parameters, such that \( \beta_{1} \) describes the effects of the \( p \) intervention package components. For centers in the control arm or for pre-intervention data, \( a = x = 0 \). We assume that in each stage, conditionally on \( A = a \) and \( z \), outcomes are independent within and between centers. Learning the intervention, however, causes dependence between stages, which we consider below.

A main goal of the LAGO design is to identify the optimal intervention package. Let \( \hat{p} \) be a pre-specified acceptable outcome probability and \( C(x) \) be a known cost function. For example, in the BetterBirth Study, one may want to find the minimal number of repeated on-site coaching visits to ensure that oxytocin is administrated to the mother right after delivery in at least 85% of births (\( \hat{p} = 0.85 \)). If \( \beta \) were known, an optimal intervention for a center with covariates \( z \) could be the solution to the center-specific optimization problem

\[
\min_{x} C(x) \quad \text{subject to} \quad p_{a}(\beta; \tilde{z}) \geq \hat{p} \quad \& \quad x \in \mathcal{X}. \tag{2}
\]

The algorithm used to solve (2), for a known or estimated value of \( \beta \), depends on the form of \( C(x) \). Under linear cost with unit costs \( c_{r} \) for the \( r \)-th component of the intervention, the solution is achieved by setting all components to their minimal value \( \mathcal{L} \), ordering the components by their cost-efficiency \( \beta_{1r}/c_{r} \), and increasing the most cost-efficient component until either \( \hat{p} \) is achieved or until this component reaches its maximal value, and then moving to the next most cost-efficient component among the remaining components. For other cost functions, standard optimization algorithms can be used. We assume that for the true parameter values, there is a unique solution to (2). For example, if the intervention has two components with unit costs \( c_{1} \) and \( c_{2} \), this means that \( \beta_{11}/c_{1} \neq \beta_{12}/c_{2} \). Alternatively to (2), another definition of an optimal intervention can be to require that the intervention results in an outcome probability \( \hat{p} \) on average over all centers instead of for each center separately.

We continue our description of the data and model with stage 1. Let \( \tilde{z}^{(1)} = (z_{1}^{(1)}, ..., z_{j_{1}}^{(1)}) \) be the observed center characteristics in each of the \( J_{1} \) stage 1 centers. Let \( x_{j}^{(1)} \) be the recommended (multivariate) intervention value for center \( j \) in stage 1. We assume that the stage 1 recommended interventions, \( x_{j}^{(1)} \)'s, are determined before the trial starts. The actual intervention in center \( j \) of stage 1 is, however, \( a_{j}^{(1)} = h_{j}^{(1)}(x_{j}^{(1)}) \), where \( h_{j}^{(1)} \)
is a deterministic center-specific continuous function from $\mathcal{X}$ to $\mathcal{X}$ that describes how center $j$ implements the actual intervention based on the recommendation $x^{(1)}_j$. We do not assume that the $h^{(1)}_j$’s are known, but that the $a^{(1)}_j$’s are observed. Let $Y^{(1)}_{ij}$ be the binary outcome of interest for patient $i$ in center $j$ of stage 1, each following model (1), and write the outcomes vector in center $j$ of stage 1, $\bar{Y}^{(1)}_j = (Y^{(1)}_{1j}, ..., Y^{(1)}_{nj_j})$. Let $\bar{a}^{(1)} = (a^{(1)}_1, ..., a^{(1)}_{J_1})$ and $\bar{Y}^{(1)} = (Y^{(1)}_1, ..., Y^{(1)}_{J_1})$ be all the stage 1 actual interventions and outcomes, respectively.

Following the stage 1 data collection, a stage 1 analysis is conducted to determine the stage 2 recommended intervention in new centers, denoted by $\hat{x}^{\text{opt,(2),n}_1}_j$, $j = 1, ..., J_2$; again, for controls the recommended intervention and the actual intervention are zero. The value $\hat{x}^{\text{opt,(2),n}_1}_j$ is chosen through a function, $g$, that takes as input the stage 1 data, the goal of the intervention, and the center-specific covariates. The function $g$ returns a recommended intervention, which is the estimated optimal intervention

\[ \hat{x}^{\text{opt,(2),n}_1}_j = g(\bar{a}^{(1)}_j, \bar{Y}^{(1)}_j, \bar{z}^{(2)}_j), \]

where $\bar{z}^{(2)}_j$ is the center-specific characteristics are in center $j$ of stage 2. For example, $\hat{x}^{\text{opt,(2),n}_1}_j$ can be obtained by solving the optimization problem given in (2) (for each center), with $\beta$ replaced by an estimator $\hat{\beta}^{(1)}$ based on the stage 1 data only. The superscript $n_1$ in $\hat{x}^{\text{opt,(2),n}_1}_j$ reminds us that the distribution of $\hat{x}^{\text{opt,(2),n}_1}_j$ changes with the stage 1 sample size $n_1$.

The actual intervention implemented in center $j$ of stage 2 is $\bar{A}^{(2),n}_j = h^{(2)}_j(\hat{x}^{\text{opt,(2),n}_1}_j)$, where $h^{(2)}_j$ are the analogues of $h^{(1)}_j$, but now for the stage 2 centers. We assume that the actual intervention in a stage 2 center only depends on $\hat{x}^{\text{opt,(2),n}_1}_j$, and not, e.g., on the number of stage 1 observations. Let $\hat{A}^{\text{opt,(2),n}_1} = (\hat{A}^{\text{opt,(2),n}_1}_1, ..., \hat{A}^{\text{opt,(2),n}_1}_{J_2})$ be the recommended interventions at all $J_2$ stage 2 centers. Once $\hat{A}^{\text{opt,(2),n}_1}$ are determined, stage 2 outcomes are collected under the actual interventions $\bar{A}^{(2),n}_j = (A^{(2),n}_1, ..., A^{(2),n}_{J_2})$. Let $Y^{(2),n}_j = (Y^{(2),n}_{1j}, ..., Y^{(2),n}_{nj_j})$ be the stage 2 outcomes in center $j$, each following model (1).

Let $\bar{Y}^{(2),n}_j = (Y^{(2),n}_1, ..., Y^{(2),n}_{J_2})$ be all the stage 2 outcomes. Our two main assumptions are

**Assumption 1.** Conditionally on $\hat{A}^{\text{opt,(2),n}_1}$, $(\bar{A}^{(2),n}_1, \bar{Y}^{(2),n}_1)$ are independent of the stage 1 data $(\hat{a}^{(1)}, \bar{Y}^{(1)})$.

**Assumption 2.** For all $j = 1, ..., J_2$, the stage 2 recommended intervention $\hat{x}^{\text{opt,(2),n}_1}_j$ converges in probability to a center-specific limit $x^{(2)}_j$.

Assumption 1 ensures that the dependence between the stage 1 data and stage 2 outcomes is solely due to the dependence of the $x^{\text{opt,(2),n}_1}_j$ on the stage 1 data. Assumption 2 implies that in the presence of more and more data under $a^{(1)}_j$, $j = 1, ..., J_1$, each of the estimated optimal intervention packages $\hat{x}^{\text{opt,(2),n}_1}_j$, $j = 1, ..., J_2$, converges in probability to a fixed value. For example, Assumption 2 will hold for a continuous function of the stage 1 maximum likelihood estimator $\hat{\beta}_1$. By Assumption 2, and continuity of the $h_j$’s, the Continuous Mapping Theorem implies that $A^{(2),n}_j = h^{(2)}_j(\hat{x}^{\text{opt,(2),n}_1}_j)$.
converges in probability to \( a_{ij}^{(2)} = h_{ij}^{(2)}(x_{j}^{(2)}) \). Under Assumption 1, and the aforementioned assumption that conditionally on the actual interventions, the outcomes do not depend on the recommended interventions, we get that in stage 2, \( pr(\bar{Y}^{(2,n_1)} \mid \bar{A}^{(2,n_1)} , \hat{x}^{opt,(2,n_1)}, \bar{z}^{(2)}, \bar{Y}^{(1)}) = pr(\bar{Y}^{(2,n_1)} \mid \bar{A}^{(2,n_1)} , \bar{z}^{(2)}) \).

In fact, the results we prove in this paper regarding the estimators calculated at the end of the study hold under any choice of function \( g \) for the recommended intervention (given by the researchers), as long as the analogues of Assumption 2 hold. That is, the recommended intervention need not be the estimated optimal intervention for the results to hold, just a function of the previous data that converges to a constant. Further details are given in Section 2 of the supplementary materials. The extension of the assumptions for general number of stages \( K > 2 \) is given in Section 3 of the supplementary materials.

### 2.2 The proposed estimator for \( \beta \) and its asymptotic properties

We estimate \( \beta \) after the \( K \) stages are concluded. For ease of development, we consider here \( K = 2 \), and cover the case of \( K > 2 \) in Section 3 of the supplementary materials.

We propose to estimate \( \beta \) by solving the estimating equation

\[
0 = U(\beta) = \frac{1}{n} \left\{ \sum_{j=1}^{J_1} \sum_{i=1}^{n_{j1}} \left( \frac{1}{A_{ij}^{(1)}} \right) \left( Y_{ij}^{(1)} - p_{A_{ij}^{(1)}}(\beta; z_{j}^{(1)}) \right) \right. \\
\left. + \sum_{j=1}^{J_2} \sum_{i=1}^{n_{j2}} \left( \frac{1}{A_{ij}^{(2,n_1)}} \right) \left( Y_{ij}^{(2,n_1)} - p_{A_{ij}^{(2,n_1)}}(\beta; z_{j}^{(2)}) \right) \right\}.
\]

In Section 2.1 of the supplementary materials, we show that the estimator \( \hat{\beta} \) that solves (3) is also a maximum partial likelihood estimator, that ignores how \( \bar{x}^{opt,(2,n_1)} \) and \( \bar{A}^{(2,n_1)} \) came about. Calculation of \( \hat{\beta} \) can be carried out using standard software for logistic regression.

Asymptotic theory for \( \hat{\beta} \) is complicated, however, by the fact that \( Y^{(1)} \) and \( (\bar{A}^{(2,n_1)}, \bar{Y}^{(2,n_1)}) \) are not independent. Thus, the score function is not a sum of independent random variables.

Let \( B \) be the parameter space for \( \beta \). A conditional expectations argument shows that the score function has mean zero when evaluated at the true value, denoted by \( \beta^* \); see Section 2 of the supplementary materials. Furthermore, we show in the supplementary materials that the two terms in (3) are uncorrelated. These properties are useful for proving that \( \hat{\beta} \) is consistent:

**Theorem 1.** Assume \( B \) is compact. Under Assumptions 1 and 2, \( \hat{\beta} \xrightarrow{p} \beta^* \).

The proof is given in Section 2.2 of the supplementary materials.

Asymptotic normality also poses a challenge due to the dependence between the two summands in \( U(\beta) \). It can be shown that \( \partial U(\beta)/\partial \beta \) converges in probability to \(-I(\beta)\), for all \( \beta \in B \), with \( I(\beta) \) given explicitly in the supplementary materials. The following theorem establishes asymptotic normality of \( \hat{\beta} \):

\[7\]
Theorem 2. Under Assumptions 1 and 2, 
\[ n^{1/2}(\hat{\beta} - \beta^*) \overset{D}{\rightarrow} N(0, I^{-1}(\beta^*)) \]  

(4)

The full proof of Theorem 2, which rests upon a novel coupling argument described below, is given in Section 2.3 of the supplementary materials. Here we outline the main parts of the proof. First, by the mean value theorem and further arguments, it can be shown that the asymptotic distribution of \( n^{1/2}(\hat{\beta} - \beta^*) \) is the same as the asymptotic distribution of 

\[ [I(\beta^*)]^{-1}n^{-1/2} \left[ \sum_{j=1}^{J_1} \sum_{i=1}^{n_{i1}} \left( \frac{1}{\hat{a}_{ij}^{(1)}} \right) \left( Y_{ij}^{(1)} - p_{\hat{a}_{ij}^{(1)}}(\beta^*; z_j^{(1)}) \right) \right] 
+ \sum_{j=1}^{J_2} \sum_{i=1}^{n_{i2}} \left( A_{ij}^{(2,n_1)} \right) \left( Y_{ij}^{(2,n_1)} - p_{A_{ij}^{(2,n_1)}}(\beta^*; z_j^{(2)}) \right) \]. 

(5)

Regarding the part of (5) that does not involve \( I(\beta^*) \), we will show that its asymptotic distribution is multivariate normal. We present a coupling argument to deal with the fact that the two summands in (5) are not independent. For each \( j = 1, ..., J_2 \), let \( Y_{ij}^{(2)} \), \( i = 1, ..., n_{j2} \), be independent Bernoulli random variables, independent of all stage 1 data, with success probability \( p_{\hat{a}_{ij}^{(2)}}(\beta^*; z_j^{(2)}) \). We construct variables \( \tilde{Y}_{ij}^{(2,n_1)} \) which, given the stage 1 data and \( A_{ij}^{(2,n_1)} \), have the same distribution as the original \( Y_{ij}^{(2,n_1)} \), but coupled (see e.g. Lindvall (2002)) with \( Y_{ij}^{(2)} \) in the following way. Let \( W_{ij} \) be independent uniform (0, 1) random variables, independent of all other variables introduced so-far. For \( p_{\hat{a}_{ij}^{(2)}}(\beta^*; z_j^{(2)}) > p_{A_{ij}^{(2,n_1)}}(\beta^*; z_j^{(2)}) \), let

\[ \tilde{Y}_{ij}^{(2,n_1)} = \begin{cases} 
0 & \text{if } Y_{ij}^{(2)} = 0 \\
0 & \text{if } Y_{ij}^{(2)} = 1 \text{ and } W_{ij} < \frac{p_{\hat{a}_{ij}^{(2)}}(\beta^*; z_j^{(2)}) - p_{A_{ij}^{(2,n_1)}}(\beta^*; z_j^{(2)})}{p_{\hat{a}_{ij}^{(2)}}(\beta^*; z_j^{(2)})} \\
1 & \text{if } Y_{ij}^{(2)} = 1 \text{ and } W_{ij} \geq \frac{p_{\hat{a}_{ij}^{(2)}}(\beta^*; z_j^{(2)}) - p_{A_{ij}^{(2,n_1)}}(\beta^*; z_j^{(2)})}{p_{\hat{a}_{ij}^{(2)}}(\beta^*; z_j^{(2)})}.
\end{cases} \]

A similar expression is given in the supplementary materials for the case \( p_{\hat{a}_{ij}^{(2)}}(\beta^*; z_j^{(2)}) \leq p_{A_{ij}^{(2,n_1)}}(\beta^*; z_j^{(2)}) \). The key property of the coupling argument is that given \( A_{ij}^{(2,n_1)} \) and the stage 1 data, the distribution of the coupled \( \tilde{Y}_{ij}^{(2,n_1)} \) is identical to the distribution of the original \( Y_{ij}^{(2,n_1)} \). Therefore, when we replace \( Y_{ij}^{(2,n_1)} \) with \( \tilde{Y}_{ij}^{(2,n_1)} \) in (5), the distribution of (5) is unaffected. In the supplementary materials, we use the coupled outcomes to show that the the part of (5) that does not involve \( I(\beta^*) \) has the same asymptotic
distribution as
\[
    n^{-1/2} \left\{ \sum_{j=1}^{J_1} \sum_{i=1}^{n_{j1}} \left( \frac{1}{z_j} \right) \left( Y_{ij} - p_{\alpha_j} (\beta^*; z_j) \right) + \sum_{j=1}^{J_2} \sum_{i=1}^{n_{j2}} \left( \frac{1}{z_j} \right) \left( Y_{ij} - p_{\alpha_j} (\beta^*; z_j) \right) \right\}.
\]

The asymptotic distribution of (6) follows from standard theory about logistic regression, because \( \alpha_j^{(1)} \) and \( \alpha_j^{(2)} \) are constants and the outcomes \( Y^{(1)} \) and \( Y^{(2)} = (Y_1^{(2)}, \ldots, Y_{J_2}^{(2)}) \) are independent, because the \( Y_{ij}^{(2)} \) are the outcomes under \( \alpha_j^{(2)} \). It can be shown that the asymptotic variance of (6) equals \( I(\beta^*) \). Combining the asymptotic normality distribution of (6) with (5) implies that (4) holds.

The asymptotic variance can be consistently estimated from the data by replacing \( \beta_j^{(2)}, \beta^*, \alpha_{j1} \) and \( \alpha_{j2} \) with \( A_j^{(2,n)}, \hat{\beta}, n_{j1}/n \) and \( n_{j2}/n \), respectively, in \( I(\beta^*) \). The asymptotic variance and its approximation are the same as if the interventions were fixed in advance and \( Y^{(1)} \) and \( Y^{(2,n)} \) were independent.

### 2.3 Hypothesis testing

A major goal of a LAGO study is to test for the overall effect of the intervention package. One way to test the null hypothesis of no overall intervention effect is to carry out a test for the subvector of \( \beta \) characterizing the effect of the intervention. That is, to test for \( H_0 : \beta_1 = 0 \) in model (1). This can be carried out based on the asymptotic normality result of Section 2.2.

Alternatively, the standard test for equal probabilities in the control and the intervention arms is valid despite the adaption of the intervention package. By Assumption 1, the dependence between the stage 2 and stage 1 data is solely due to the stage 1 data determining the stage 2 recommended intervention, which, in turn, affects the actual stage 2 intervention, and thus the stage 2 outcomes. However, under the null, there is no effect of the actual intervention on the stage 2 outcomes. Therefore, under the null, regardless of the way the intervention was adapted, the stage 1 and stage 2 outcomes are independent. Thus, the standard test for equal probabilities in the control and the intervention arms is valid.

An alternative, possibly more powerful, test for the overall effect of the intervention in the presence of center characteristics is to consider \( H_0 : \gamma = 0 \) in the model logit \( \tilde{p}_Q(\beta, \gamma; z) = \beta_0 + \beta_1 z + \gamma Q \), where \( Q \) is a group indicator that equals one for the intervention group and zero for the control. As before, in light of the between-stages independence under the null, \( \beta_1 = 0 \) in model (1) implies \( \gamma = 0 \). Therefore, a standard test for the hypothesis \( H_0 : \gamma = 0 \) is valid test for \( H_0 : \beta_1 = 0 \). A simulation study confirmed these statements in finite samples; see Section 5.2 of the supplementary materials.

### 2.4 Confidence sets and confidence bands

After the conclusion of the study, the optimal intervention is estimated as the solution to (2) with \( \beta \) replaced by its estimator \( \hat{\beta} \). We propose a simple procedure to find a 95%
We propose a method to develop confidence bands for the outcome probabilities of intervention packages in $X$. We calculate a 95% confidence interval for $\logit(p_x(\beta^*; z))$, i.e. for $(1 x^T \hat{z}^T)\beta^*$:

$$CI_x = \left[ (1 x^T \hat{z}^T)\hat{\beta} - 1.96\sigma(\hat{\beta}; x, \hat{z}), \quad (1 x^T \hat{z}^T)\hat{\beta} + 1.96\sigma(\hat{\beta}; x, \hat{z}) \right],$$

where $\sigma^2(\hat{\beta}; x, \hat{z}) = (1 x^T \hat{z}^T)n^{-1}I^{-1}(\hat{\beta})(1 x^T \hat{z}^T)^T$ is the estimated variance of $(1 x^T \hat{z}^T)\hat{\beta}$, and $n^{-1}I^{-1}(\hat{\beta})$ is the estimated variance of $\hat{\beta}$. The 95% confidence interval for $p_x(\beta^*; \hat{z})$ is $CI_{p_x} = \expit(CI_x)$. We then obtain the confidence set for the optimal intervention $CS(x^{opt}) = \{ x : CI_{p_x} \ni \hat{p} \}$. That is, $CS(x^{opt})$ includes intervention packages for which $\hat{p}$ is inside the confidence interval for the success probability under those interventions.

To show that the confidence set $CS(x^{opt})$ contains $x^{opt}$ with the specified probability of 0.95, recall that $p_{x^{opt}}(\beta^*; \hat{z}) = \expit[(1 x^{optT} \hat{z}^T)\beta^*] = \hat{p}$. Therefore,

$$Pr(CS(x^{opt}) \ni \hat{x}^{opt}) = Pr(CI_{p_{x^{opt}}} \ni \hat{p} = Pr(CI_{p_{x^{opt}}} \ni p_{x^{opt}}(\beta^*; \hat{z})) = 0.95.$$

Implementing this procedure is simple and its calculation is fast. Because calculating $CS(x^{opt})$ does not depend upon estimating $x^{opt}$, it does not involve the optimization algorithm.

At the end of the study, researchers might be interested in a variety of potential intervention packages in $X$ that were not necessarily marked as of interest a priori. We propose a method to develop confidence bands for the outcome probabilities $p_x(\beta; \hat{z})$ for a range of $x \in X$ of interest, simultaneously. These confidence bands allow researchers to study the entire intervention space when comparing potential choices of the intervention package. We propose a procedure that is based on the asymptotic normality of $\hat{\beta}$ and on Scheffé’s method (Scheffé, 1959). First, for all $x \in X$, construct $CB_x$ to obtain 95% confidence bands for $\{ (1 x^T \hat{z}^T)\beta^* : x \in X \}$,

$$CB_x = \left[ (1 x^T \hat{z}^T)\hat{\beta} - \chi^2_{0.95,p+q+1}(\hat{\beta}; x, \hat{z}), \quad (1 x^T \hat{z}^T)\hat{\beta} + \chi^2_{0.95,p+q+1}(\hat{\beta}; x, \hat{z}) \right],$$

with $\sigma(\hat{\beta}; x, \hat{z})$ defined as before and $\chi^2_{0.95,p+q+1}$ the 95% quantile of a $\chi^2_{p+q+1}$ distribution. As before, we transform $CB_x$ into confidence bands for $p_x(\beta; \hat{z})$ by setting $CB_{p_x} = \expit(CB_x)$. These confidence bands guarantee asymptotic simultaneous 95% coverage for all possible intervention package compositions; see Section 4 of the supplementary materials.

### 3 Simulations

We carried out simulation studies to investigate the finite sample properties of our estimators and methods. We simulated 1000 datasets per simulation scenario. We considered a two-stage LAGO design with equal number of centers per stage $J$, with half the centers in the intervention arm and half in the control arm. The total sample size available at the end of the study is $J(n_{1j} + n_{2j})$. We considered the values $J = 6$, 10, 20,
The intervention had two components, $\mathbf{x} = (x_1, x_2)$, with unit costs $c_1 = 1$ and $c_2 = 8$. The minimum and maximum values of $X_1$ and $X_2$ were $[L_1, U_1] = [0, 2]$ and $[L_2, U_2] = [0, 5]$. We considered the following values for $\exp(\beta^*_1) = (\exp(\beta^*_{11}), \exp(\beta^*_{12})): (1, 1)$ (the null), $(1, 1.2), (1, 1.5), (1.2, 1.5)$, and $(1.2, 2)$. A single center covariate $z$ was normally distributed with mean 0 and variance 1 and its coefficient was taken to be $\beta_2^* = \log(0.75)$. For simplicity, we did not include an intercept in the model, although each center had its own baseline success probability due to $z$. For $z = 0$, the probability of success in the control arm was 0.5. The stage 2 recommended intervention was based on solving the optimization problem (2) using the stage 1 estimates of $\beta$. Technical details on what we did when no solution existed for which $\tilde{p}$ was reached are given in Section 5.1 of the supplementary materials.

Selected results are presented in Tables 1 and 2. Table 1 shows that for $J > 6$, the finite sample bias was minimal, the mean estimated standard error was very close to the empirical standard deviation, and the empirical coverage rate of the confidence intervals for the effects of the individual package components was very close to 95%. Moreover, Section 5.2 of the supplementary shows that the type I error of the tests presented in Section 2.3 was close to 0.05.

Table 2 presents results for the optimal intervention and success probabilities, for $J = 20$ and calculated for a typical center with $z = 0$; results for $J = 6, 10$ are presented in Section 5.2 of the supplementary materials. The finite sample bias and the root mean squared errors of the final $\hat{x}^{opt}$ were generally small and decreased as the number of centers per stage and the sample size increased. The nominal coverage rate of the confidence set $CS(\hat{x}^{opt})$ was approximately 95%, with the set typically including between 3 to 14 percent of $\mathcal{X}$. We also compared the cost of the estimated optimal intervention to the cost of the true optimal intervention and found it to be almost the same for the scenarios presented in Table 2; see the supplementary materials. The empirical coverage rate of the confidence bands for $p_\mathbf{x}(\beta^*; z = 0)$ was very close to 95%.

4 Illustrative example

The BetterBirth Study consisted of three stages. The first two stages were pilot stages to develop the intervention package. Stage 3 was a randomized controlled trial. The development of the recommended intervention package was done qualitatively, as described in Hirschhorn et al. (2015), and the intervention package was adjusted after each pilot stage. The results of the randomized controlled trial were presented and discussed in Semrau et al. (2017). The number of centers in the first, second, and third stages was 2, 4 and 30, respectively. In the first two stages, data in each center were collected before and after the intervention was implemented. In stage 3, there were 15 centers in the control arm and 15 centers in the intervention arm. In 5 intervention arm centers, outcome data were also collected before the intervention was implemented.

Here we focus on the binary outcome of oxytocin administration immediately after delivery, as recommended by the WHO (WHO, 2012) to prevent postpartum hemorrhage, a major cause of maternal mortality. The intervention package components were
| exp(β\*\( \times 100 \)) | \( n_{1j} \) | \( n_{2j} \) | \( J \) | \%RelBias | SE/EMP.SD | CP95 | \%RelBias | SE/EMP.SD | CP95 |
|---|---|---|---|---|---|---|---|---|---|
| (1.2, 1.5) | 50 | 100 | 6 | -1.1 | 92.0 | 95.2 | -2.1 | 83.3 | 94.2 |
| &nbsp; | 10 | -3.0 | 100.1 | 95.6 | -0.8 | 93.4 | 94.9 |
| &nbsp; | 20 | 0.1 | 103.5 | 95.5 | -0.6 | 104.9 | 96.1 |
| &nbsp; | 200 | 6 | -3.0 | 88.4 | 94.9 | -3.1 | 83.5 | 95.2 |
| &nbsp; | 10 | -6.6 | 92.9 | 94.5 | -0.9 | 93.5 | 94.9 |
| &nbsp; | 20 | 0.2 | 102.5 | 95.6 | -0.6 | 97.7 | 95.3 |
| &nbsp; | 100 | 100 | 6 | -0.8 | 89.5 | 95.1 | -1.6 | 86.7 | 95.2 |
| &nbsp; | 10 | 3.5 | 102.2 | 95.7 | -1.3 | 102.2 | 95.0 |
| &nbsp; | 20 | 1.5 | 100.7 | 95.3 | -0.4 | 101.1 | 95.2 |
| &nbsp; | 200 | 6 | -2.2 | 90.4 | 94.6 | -1.4 | 89.7 | 96.0 |
| &nbsp; | 10 | -0.8 | 102.7 | 96.7 | -0.7 | 95.9 | 95.5 |
| &nbsp; | 20 | -0.3 | 97.4 | 94.7 | -0.4 | 96.7 | 94.1 |
| (1.2, 2) | 50 | 100 | 6 | -11.4 | 89.0 | 94.8 | -0.4 | 82.2 | 96.1 |
| &nbsp; | 10 | -7.3 | 103.7 | 95.7 | 0.4 | 104.4 | 96.5 |
| &nbsp; | 20 | -3.1 | 99.0 | 94.7 | -0.1 | 100.8 | 95.0 |
| &nbsp; | 200 | 6 | -15.8 | 92.6 | 95.0 | 1.4 | 89.7 | 94.9 |
| &nbsp; | 10 | -8.1 | 93.3 | 95.7 | 0.3 | 99.6 | 95.5 |
| &nbsp; | 20 | -1.8 | 100.1 | 95.3 | -0.5 | 102.5 | 96.6 |
| &nbsp; | 100 | 100 | 6 | -6.0 | 96.2 | 96.3 | 0.0 | 94.0 | 95.2 |
| &nbsp; | 10 | -2.7 | 98.2 | 95.1 | -0.2 | 104.7 | 95.4 |
| &nbsp; | 20 | -2.7 | 100.7 | 95.2 | 0.2 | 102.2 | 95.2 |
| &nbsp; | 200 | 6 | -8.9 | 95.4 | 95.4 | 0.3 | 83.8 | 96.5 |
| &nbsp; | 10 | -5.0 | 95.6 | 94.6 | 0.0 | 97.3 | 95.3 |
| &nbsp; | 20 | -3.2 | 98.9 | 94.4 | 0.1 | 104.7 | 95.5 |

%RelBias, percent relative bias \( 100(\hat{\beta} - \beta^*)/\beta^* \); SE, mean estimated standard error; EMP.SD, empirical standard deviation; CP95, empirical coverage rate of 95% confidence intervals.
Table 2: Simulation study: results for estimated optimal intervention package and coverage of 95% confidence bands for success probabilities. Unit costs were $c_1 = 1$ and $c_2 = 8$. Results presented for $J = 20$ centers per stage.

| $\exp(\beta^*)$ | $x^{opt}$ | $n_{ij}$ | $n_{2j}$ | Bias($x^{opt}_{1j}$) | Bias($x^{opt}_{2j}$) | RMSE($x^{opt}$) | SetCP95 | SetPerc% | BandsCP95 |
|------------------|-----------|---------|---------|----------------------|----------------------|----------------|---------|---------|-----------|
|                  |           |         |         | ($\times 100$)       | ($\times 100$)       | ($\times 100$)  |         |         |           |
| (1, 2)           | (0, 3.2)  | 50      | 100     | -36.4                | -5.0                 | 87.3           | 94.8    | 7.6     | 96.9      |
|                  |           | 500     | 100     | 18.6                 | -2.4                 | 62.0           | 95.2    | 4.1     | 96.8      |
|                  |           | 100     | 100     | 22.6                 | -2.8                 | 69.0           | 94.5    | 6.1     | 96.7      |
|                  |           | 500     | 100     | 9.8                  | -1.3                 | 45.3           | 94.5    | 3.7     | 97.5      |
| (1.2, 1.5)       | (2, 4.5)  | 50      | 100     | -8.4                 | 2.4                  | 48.9           | 94.4    | 13.3    | 96.8      |
|                  |           | 500     | 100     | -1.9                 | 0.9                  | 25.0           | 94.9    | 7.7     | 95.9      |
|                  |           | 100     | 100     | -4.4                 | 1.3                  | 38.4           | 94.6    | 12.3    | 95.5      |
|                  |           | 500     | 100     | -0.6                 | 2.2                  | 18.4           | 94.8    | 7.1     | 95.5      |
| (1.2, 2)         | (2, 2.6)  | 50      | 100     | -31.2                | 4.0                  | 81.6           | 94.0    | 14.2    | 95.0      |
|                  |           | 500     | 100     | -15.2                | 3.3                  | 57.1           | 94.9    | 8.0     | 94.8      |
|                  |           | 100     | 100     | -21.8                | 2.7                  | 68.3           | 95.1    | 12.4    | 95.4      |
|                  |           | 500     | 100     | -9.0                 | 2.6                  | 44.1           | 94.3    | 7.5     | 95.0      |

RMSE, root of mean squared errors \{$\text{mean}([|\hat{x}^{opt} - x^{opt}|^2])^{1/2}$, mean taken over simulation iterations; SetCP95, empirical coverage percentage of confidence set for optimal intervention; SetPerc%, mean percent of $X$ covered by the confidence set; BandsCP95, empirical coverage rate of 95% confidence bands for $\{p_x(\beta; z = 0) : x \in X\}$.

the duration of the on-site intervention launch (in days), the number of coaching visits after the intervention was launched, the leadership engagement (non-standardized initial engagement, standardized initial engagement, and standardized initial engagement with follow-up visits) and the data feedback form (categorical: none; ongoing, paper-based; ongoing app-based). The four components were adapted in a way that resulted in almost perfect multicollinearity. Therefore, for illustration purposes, we considered the first two components only, launch duration and number of coaching visits. The launch duration was 3 days in stage 1 and 2 days in stages 2 and 3. Compared to stage 1, the intensity of coaching visits was increased in stage 2, and further increased in stage 3. For illustrative purposes, we truncated the data at 40 coaching visits or less. The center baseline characteristic we used was the approximate monthly birth volume, given that large facilities might be likely to follow WHO recommendations about oxytocin administration more closely, regardless of the implemented intervention package. Other available center characteristics, e.g. number of staff nurses, were highly correlated with the monthly birth volume.

Table 3 provides the results of the logistic regression after each of the stages, using all available data at that point. The sample size in stage 1 was relatively small, explaining the wide confidence intervals for the odds ratios. The final results imply that both package components had an effect. Tests for the overall effect of the package yielded a highly significant p-value, regardless of the test we used.

Regarding the cost, after consulting with the study investigators, we assigned unit costs of $800 per launch day and $170 per coaching visit. In practice, implementation costs may also depend on center size and then $C(x)$ could be replaced with $C_z(x)$.

The estimation of the optimal intervention package with linear cost $C(x) = c_1 x_1 + c_2 x_2$. 

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Table 3: Package component effect estimates and confidence intervals, calculated after each stage.

|                           | Stage 1 \((n_1 = 73)\) | Stages 1-2 \((n_1 + n_2 = 1780)\) | Stages 1-3 \((n_1 + n_2 + n_3 = n = 6124)\) |
|---------------------------|-------------------------|-------------------------------------|-----------------------------------------------|
|                           | \(\hat{\beta} \) (OR) | CI-OR                               | \(\hat{\beta} \) (OR) CI-OR                  | \(\hat{\beta} \) (OR) CI-OR                  |
| Intercept                 | 0.07 (1.07)             | (0.00, 280.80)                      | -2.27 (0.10)                                 | (-0.07, 0.15)                                 | -2.30 (0.10)                                 | (-0.09, 0.11)                                |
| Coaching Visits (per 3 visits) | 2.07 (7.95)          | (1.77, 73.95)                       | 0.11 (1.11)                                 | (0.96, 1.28)                                 | 0.08 (1.08)                                 | (1.04, 1.12)                                |
| Launch Duration           | -1.00 (0.37)            | (0.00, 32.33)                       | 0.75 (2.11)                                 | (1.93, 2.33)                                 | 0.66 (1.94)                                 | (1.84, 2.06)                                |
| Birth Volume (monthly, per 100) | -1.00 (1.41)         | (0.76, 2.64)                        | 0.97 (2.65)                                 | (1.95, 3.77)                                 | 1.02 (2.79)                                 | (2.41, 3.23)                                |

\(\hat{x}_{opt,2,n_1} = (1, 5)\) \(\hat{x}_{opt,3,(n_1,n_2)} = (3, 1)\) \(\hat{x}^{opt} = (3, 1)\)

OR, estimated odds ratio \(\exp(\hat{\beta})\); CI-OR, 95% Confidence interval for the odds ratio. In the estimated optimal interventions, the first component is the number of coaching visits and the second component is the launch duration (in days).

c_{2}x_{2} was conducted as in the simulation study. Assuming that at least 1 launch day and 1 coaching visit are needed, and that a launch duration of more than 5 days or having more than 40 coaching visits is impractical, we estimated the optimal intervention for a center with average birth volume \((z = 175)\) to be a launch duration of 2.78 days and 1 coaching visit. We also carried out optimization over combinations of all possible discrete values, which are 1, ..., 40 coaching visits and 1, 1.5, 2, 2.5, ..., 5 for duration of intervention launch. This led us to estimate the optimal intervention as launch duration of three days with one coaching visit, \(\hat{x}^{opt} = (3, 1)\). The total cost of the estimated optimal intervention package, \(\hat{x}^{opt} = 2570\).

We calculated a 95% confidence set for the optimal intervention \(CS(x^{opt})\) over the grid of \(X\), taking all possible numbers of coaching visits, 1, ..., 40, and 1, 1.5, 2, 2.5, ..., 5 for intervention launch duration. Out of 360 potential intervention packages, 38 (10.5%) were included in the confidence set. The set included the following combinations: 1.5 days launch duration and 40 coaching visits; 2 days launch durations and 27 or more coaching visits; 2.5 days launch duration and less than 20 coaching visits; and 3 days launch duration and less than 5 coaching visits. The first, second and third quartiles of the cost distribution within \(CS(x^{opt})\) were \(Q1 = $2462\), \(Q2 = $4035\), and \(Q3 = $6797\). We also calculated 95% simultaneous confidence bands for the probability of success under all 360 intervention compositions; plots are shown in Section 6 of the supplementary materials. For the estimated optimal intervention \(\hat{x}^{opt} = (1, 3)\), the obtained interval for the probability of oxytocin administration was \((0.79, 0.93)\). The mean difference between the top and bottom of the confidence band was 0.07.

5 Discussion

We developed the LAGO design for multiple component intervention studies with a binary outcome, where the intervention package composition is systematically adapted as part of the design. The goals of studies using the LAGO design are to find the optimal intervention package, to test its effect on the outcome of interest, and to estimate its
effect as well as the effects of the individual components

The methodology in this paper was developed for scenarios with a stagewise analysis that does not include formal hypothesis testing. However, the LAGO design allows for futility stops, since stopping the trial for futility between stages preserves the type I error. The type I error can only decrease from the nominal level when futility stops are included (Snapinn et al., 2006).

For clear presentation of the design, methods, and theory, we focused on a general yet practical design. Our work opens the way for further research. For example, it would be interesting to develop methods for studies with further dependence because centers contribute data to more than one stage. The results in this paper could also be extended to continuous, count, or survival outcome data. In this paper, we focused on treating variation between centers using measured center characteristics. A potential extension could consider a random effect for each center.

Many large effectiveness and implementation trials fail because current design methodology does not permit adaptation in the face of implementation failure as in, for example, the BetterBirth (Semrau et al., 2017) and TasP (Iwuji et al., 2017) studies. The LAGO design rigorously formalizes practice in public health research that are presently conducted in an ad hoc manner, with unknown consequences for the validity of subsequent standard analysis (Escoffery et al., 2018). We expect widespread use of the design as a result, with potential gain for many randomized clinical trials.

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