REMATCHING ON-THE-FLY: SEQUENTIAL MATCHED RANDOMIZATION AND A CASE FOR COVARIATE-ADAPTIVE RANDOMIZATION

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ABSTRACT

Background: Sequential Matched Randomization (SMR) is one of multiple recent covariate-adaptive randomization (CAR) procedures that utilize a distance matrix to improve covariate-balance and estimation efficiency. Randomization occurs within mates whose distance meet an a-priori, fixed similarity quantile of random distances.

Methods: We extend SMR to allow multiple participants to be randomized simultaneously, to allow matches to break and rematch if a better match later enrolls (Sequential Rematched Randomization; SRR), and to use a dynamic threshold. In simplified settings which vary covariate distribution and association upon outcome, we compare end-study covariate-balance and estimator efficiency in SMR before and after extensions. In a real-world application, we compare covariate-balance, power, and estimator efficiency of SMR before and after extensions when adjusting for priority covariates and all covariates of interest. We compare with Complete Randomization (CR) and CR followed by a flexible, covariate-adjusted regression model. As side-by-side comparisons, we include stratified randomization, $D_A$ optimality biased coin design ($D_A$-BCD), and Pairwise Sequential Randomization (PSR).

Results: In both the simplified and real-world application, we observe benefits of each extension upon covariate balance and estimator efficiency. In the real-world application, SRR with a dynamic threshold, $D_A$-BCD, and PSR provide greater power than CR followed by a covariate-adjusted regression model. Matching methods achieved greater covariate-balance when adjusting for all covariates yet greater power and efficiency when adjusting for priority covariates.

Conclusion: We improve upon SMR and show the potential for CAR methods – that adjusting for covariates in randomization can outperform covariate adjustment in a flexible regression model.

1 Introduction

This past decade has seen major advancements in covariate-adaptive randomization (CAR). The use of a distance matrix has been incorporated into Matched Randomization (MR)\cite{1,2} and Sequential Matched Randomization (SMR)
We denote a study as having enrolled with and without extensions. We consider adjusting for priority covariates and all covariates of interest, and we compare As a point of reference, we highlight two other CAR procedures which aim to increase covariate balance and power to with a non-null treatment effect and in which covariates were linearly and non-linearly associated with a normal were generally impressed by the performance of CAR schemes in balancing covariates and increasing efficiency. A second purpose arose to present a case study which highlights the potential benefits of adjusting for covariates in CAR rather than a regression model in a moderately large randomized clinical trial (n of 512).

SMR uses the matching on-the-fly algorithm to form two-person pairs (or strata) of participants and to randomize treatment within pairs. An initial set of participants are randomized using Complete Randomization (CR) at enrollment one-at-a-time. They form a “reservoir” of participants who have been randomized but, as of yet, have not matched with another participant. Once a reservoir of pre-specified size has built up, subsequent participants are compared to reservoir members on baseline covariates using a distance matrix – typically Mahalanobis Distance. The entering participant becomes “mates” with their best reservoir match if they meet a pre-specified matching-threshold of distance similarity, and the entering participant receives the treatment opposite to their mate. Both are then excluded from the reservoir of potential mates. If, however, the best reservoir match is not similar enough, the entering participant is randomized under CR and joins the reservoir awaiting a mate. By the end of the study, some participants may not have found a mate, and treatment allocation may be imbalanced. In its development, SMR was studied in simulations with a non-null treatment effect and in which covariates were linearly and non-linearly associated with a normal outcome. SMR was more powerful than stratified randomization and Begg and Iglewicz’s minimization with a biased coin. The SMR algorithm has also been extended to prioritize covariate balance based upon their association with the outcome. This dramatically improves power in settings where outcomes are assessed before the next participant enrolls. In this work, we do not focus exclusively on this setting.

As a point of reference, we highlight two other CAR procedures which aim to increase covariate balance and power to detect a treatment effect: $D_A$ minimization with a biased coin design ($D_A$-BCD) and PSR. $D_A$-BCD randomizes participants to the arm which minimizes the standard error of the treatment effect under a pre-specified regression model. The objective is to minimize the orthogonality between covariates and the treatment. $D_A$-BCD refines Begg and Iglewicz’s minimization by not requiring continuous covariates to be categorized. PSR is similar in spirit to SMR; however, it randomizes with a biased coin to the arm which minimizes the overall Mahalanobis Distance (as compared to finding matches within the distance matrix).

Our work to improve upon SMR and to highlight the strengths of CAR procedures proceeds as follows. First, we introduce notation used throughout. Second, we propose SMR extensions on (i) allowing batch enrollment, (ii) allowing matches to break and rematch (Sequential Rematched Randomization; SRR), and (iii) using a dynamic matching-threshold with control for chronological bias. Third, in simplified settings that vary covariate distribution, covariate association with outcome, and sample size, we compare SMR under a range of fixed matching-thresholds to SMR with extensions. Fourth, in a real-world application, we compare covariate balance, power, and estimator efficiency of SMR with and without extensions. We consider adjusting for priority covariates and all covariates of interest, and we compare to CR and CR followed by a flexible covariate-adjusted regression model. As a side-by-side comparison, we include the performance under stratification, $D_A$-BCD, and PSR. We end with final conclusions and discussions.

2 Notation

We denote a study as having enrolled $n = 1, \ldots, N$ participants throughout $b = 1, \ldots, B$ batches of sequential enrollment. At the $b^{th}$ batch of enrolling participants, the set of unmatched participants is denoted as $U_b$ and the number of participants in the set is denoted as $|U_b|$. Let $|R_b|$ be the number of expected remaining study entrants. In general, CAR schemes are adjusted to $p$ baseline covariates which may include dummy variables for categorical covariates.

Common SMR practice uses Mahalanobis Distance and builds the initial reservoir to $p+2$ participants. The pre-specified matching-threshold is based on a quantile from a reference distribution of randomly matched distances, which we denote as $F$ and $F_b$ following a given batch of enrollments. $F_b$ is commonly estimated as $F_b$ using the parametric $F(p,n,p)$ distribution, though $F_b$ may be estimated empirically by bootstrap sampling a random set of $n/2$ matches from the upper- (or lower-) triangle of the distance matrix. The notation SMR(E, Q) and SMR(F, Q) respectively denote using SMR with the quantile Q as a matching-threshold of $F_b$ estimated either empirically or by $F(p,n,p)$.
3 Extensions to SMR

3.1 Batch matching

SMR requires participants to be randomized one at a time. A fully sequential matching scheme "greedily" finds the best mates at the moment although a better mate may later exist. In contrast, MR randomizes all participants or units in a single batch within the set of mates that minimize the total sum of matched distances. Applying this optimality criteria, we extend SMR for randomization of any batch size. As multiple participants enroll, potential mates are found which minimize the total sum of matched distances. Randomization occurs within potential mates that meet the matching threshold. The R nbpMatching package finds optimal sets of potential mates. MR is a special case of SMR with \( B = 1 \) and is the least greedy of SMR schemes.

3.2 Sequential Rematching

Throughout enrollment, SRR allows mates to break and rematch to participants who do not share the same treatment assignment. It aims to, at least partially, recover some of the loss in MR optimal matches. We call the SRR algorithm rematching on-the-fly or sequential rematching.

3.3 Dynamic matching-threshold with chronological bias control

Determining an appropriate fixed matching-threshold may be challenging. An overly strict fixed matching-threshold would yield no matches and in turn may be no better than CR. In contrast, an overly relaxed matching-threshold would degenerate to a block-two randomization scheme vulnerable to subversion bias. We propose a dynamic matching-threshold reflecting the chance of matching an existing reservoir member considering existing and future possible mates. Formally, this is the quantile \( Q_b \) of \( \hat{F}_b \) where

\[
Q_b = \frac{||U_b|| - 1}{||U_b|| + ||R_b|| - 1}.
\]

When estimating \( \hat{F}_b \) with bootstrap sampling, the dynamic matching-threshold is the averaged \( Q_b \) percentile across bootstrap samples of \( \hat{F}_b \). To achieve equal treatment allocation, the matching-threshold for matches may be removed when the reservoir size is the same or less than the number of participants left to enroll. The dynamic matching-threshold is then:

\[
\text{Threshold}_b = \left\{ \begin{array}{ll}
\hat{F}_b^{-1}(Q_b) & ||U_b|| < ||R_b|| \\
\text{best match(es)} & ||U_b|| \geq ||R_b||
\end{array} \right.
\]

To control for potential chronological bias, we implement SMR using a Maximum Tolerable Imbalance (MTI) procedure. Under the Big Stick Design, a non-matching participant is randomized so long as the allocation between treatment groups does not exceed a pre-specified treatment allocation imbalance. We allow matches to occur even if it would lead to an imbalance greater than pre-specified; however, this is easily amendable as part of the dynamic matching-threshold rule. MTI procedures are preferred over Permuted Blocks because they are less predictable (i.e. have greater encryption).

3.4 Comment: Imputing missing baseline characteristics

As with many CAR schemes, SMR and SRR require a complete set of baseline covariates to carry out randomization; yet, this may not always be feasible. For example, an important baseline lab value may take more time to process than desired for randomization. The nbpMatching R package used for batch matching may also be used to facilitate imputation of missing baseline covariates. We do not attempt to investigate the performance of imputing missing baseline covariates in this work. However, we mention the feature of imputing missing baseline covariates because it played a critical role when SMR was used in the real-life application presented later.

4 Simulations under simplified settings

In simplified settings that condition SMR on two covariates, we sought to find fixed matching-thresholds that yielded optimal covariate balance and estimation efficiency and to assess the benefit of the proposed extensions. We hypothesized that (H1) the optimal, SMR fixed matching-threshold would be sensitive to covariate distribution, covariate association with outcome, and sample size and that (H2) each extension, individually and potentially collectively, would improve covariate balance and estimator efficiency.
Standard normal outcomes were simulated such that two covariates each explained 10% (mild) and/or 25% (moderate) outcome variability. The first of the covariates was standard normal, and the second followed one of three distributions (CD1) dichotomous with 20% prevalence, (CD2) dichotomous with 50% prevalence, and (CD3) standard normal. For each covariate distribution setting, we considered four covariate predictive settings for the two covariates: (CP1) moderate and moderate, (CP2) mild and moderate, (CP3) moderate and mild, (CP4) mild and mild. Setting CD1+CP3 reflects situations when there is a moderately-associated continuous covariate and a mildly-associated, and somewhat rare, dichotomous covariate.

Each combination of settings were evaluated with $N$ of 50 and 250 for a total of 24 simulation settings. Each setting was replicated to generate 50K datasets. CR, MR (the upper limit potential of sequential batch randomization), SMR and SRR were carried out for each simulated dataset. Fixed matching-thresholds ranged from 5% to 50% of the $\binom{p}{n-p}$ distribution. The dynamic threshold included an MTI of 4. We estimated the average absolute standardized mean difference (SMD) of each covariate across replicates and the standard deviation of the difference of outcome means estimated from each replicate. Covariate-balance and estimator efficiency results are respectively presented in Figure 1 and 2.

H1: Under SMR, there was a U-shaped balance and efficiency curve that became less sensitive with increased sample size – especially for lower matching-thresholds. For covariate balance, the optimal matching-threshold for continuous covariates (CD3) decreased with sample size from about 30% (n = 50) to about 15% (n = 250) to about 5% in the presence of a categorical covariate (CD2 with n = 250). The optimal matching-threshold for balancing categorical covariates generally remained at 30-40% regardless of sample size and other covariate distribution. For estimator efficiency, it was worse to have an extreme large matching-threshold than an extreme than small matching-threshold (i.e. 50% vs 5%; exception CD3 with n = 50). Having a categorical covariate seemed to taper the diminished returns of a large matching-threshold (50% matching-threshold of CD1 and CD2 vs CD3). In general, a matching-threshold of 10-20% was a reasonable compromise for optimizing covariate balance and estimator efficiency across settings.

H2 (SMR with dynamic threshold): For continuous covariate balance, SMR performed better with a dynamic matching-threshold than with fixed matching-thresholds. For categorical covariate balance and estimator efficiency, SMR with a dynamic matching-threshold was at least comparable and more often superior to using a fixed matching-threshold.

H2 (SMR vs MR and SRR): Covariate balance and efficiency was best under MR, followed by SRR, then SMR for a given covariate distribution, covariate association, sample size, and fixed matching-threshold. When using a dynamic threshold the ranking changed to MR, SMR, then SRR. Also, when balancing categorical covariates in CD2, SRR surpassed MR when using a fixed matching-threshold of at least 30%. In most settings SRR with a dynamic threshold had comparable efficiency as SMR with a fixed matching-threshold of 10-20%; in an exception, SMR with a fixed threshold was more clearly efficient in settings with a more strongly associated categorical covariate (i.e. CD1+CP2 and CD2+CP2).

As general conclusions of these simplified settings, the optimal, fixed matching-threshold for SMR was sensitive to covariate distribution and association upon outcome, especially for smaller sample sizes and in the absence of categorical covariates. In these simulations, a fixed matching-threshold of about 10-20% was generally in the sweet spot for optimizing SMR covariate balance and estimator efficiency. In almost all scenarios, using SMR with a dynamic matching-threshold further improved upon covariate-balance and estimator efficiency compared to SMR with a fixed matching-threshold in this sweet spot. We also saw benefits of batched randomization (through the performance of MR) and SRR compared to SMR with a fixed threshold. Based on covariate-balance results, it may be tempting to consider SRR with a generous threshold. However, the U-shaped efficiency curve for SRR suggests this to be overall counterproductive.

5 Application to REACH trial

The Rapid Education/Encouragement And Communications for Health (REACH) randomized clinical trial provided text message-delivered diabetes support to help adults with type 2 diabetes improve glycemic control and adhere to treatment medication. 512 Participants enrolled and were randomized across three treatment arms with a 2:1:1 allocation ratio: enhanced treatment as usual (a text message when study A1c results are available), frequent diabetes self-care support text messages, and frequent diabetes self-care support text messages with monthly phone coaching. At baseline, clinical and demographic covariates were collected that may be associated with the outcome 12-month Hemoglobin A1c (HbA1c), including site (community clinic versus Vanderbilt University Medical Center primary care), HbA1c, age at enrollment, gender, years of education, years of since diabetes diagnosis, race / ethnicity, medication type, income, and type of health insurance. Baseline characteristics and study results are published elsewhere [20].
Randomization often occurred before all baseline covariates could be collected. Notably, baseline HbA1c generally took additional processing time. In this study, clinical coordinators enrolled participants and sent baseline data to the statistician for weekly batch randomization via REDCap [21, 22]. Using the npMatching package, missing baseline covariates were imputed and SMR with batch randomization was utilized. Once HbA1c was available, it was updated and included in future SMR randomizations.

With a complete set of REACH baseline characteristics, we wished to compare the ability of SMR, with and without extensions, to increase covariate balance and estimator efficiency. For simplicity, we supposed the study was a 1:1 trial comparing usual care to either of the intervention arms. The base SMR comparators included SMR(E, 20) and SMR(F, 20). We carried out SMR extensions as SMR(E, D), SMR(F, D), SRR(E, 20), SRR(F, 20), SRR(E, D), and SRR(F, D). MR was included reflecting the potential of sequential batched randomization and the potential loss under fully-sequential matching. We were interested in adjusting for two sets of baseline covariates. Priority covariates included baseline HbA1c, medication type, and time since diabetes diagnosis ($R^2 = 0.26$ with 12-month HbA1c). The second set conditioned on all aforementioned baseline covariates ($R^2 = 0.32$ with 12-month HbA1c). We used 200 bootstrap samples for estimating $F_b$ empirically and found conclusions to be consistent as when using 1000 bootstrap samples (data not shown).

As a side-by-side comparison, we compared performance with CR, stratified randomization, $D_{A-BCD}$ (3/4 biased coin), and PSR (3/4 biased coin). The $D_{A-BCD}$ regression model was pre-specified with first to third degree polynomials on continuous covariates to allow for non-linear associations with the outcome and used the generalized inverse when there were fewer participants than degrees of freedom [23]. We used the PSR coding made available in existing literature [10]. Stratified randomization used categorized derivations of baseline HbA1c (<7.0%, 7.0-8.0%, 8.0%+), age ($\leq 60$, >60), years of education ($\leq 12$, >12), and time since diabetes diagnosis ($<10$, $\geq 10$ years).

For each randomization scheme, we kept baseline covariates fixed as observed in the REACH trial and generated random outcomes under the potential outcomes framework. First, via rerandomization we generated 50K randomization sequences. Then, for each randomization sequence, we imposed a sharp treatment effect of 0, -0.15, -0.3, and -0.5 (lower HbA1c is better), yielding 50K outcome datasets per sharp treatment effect. For each outcome dataset, we carried out RBI using the 50K randomization sequences and recorded the estimated effect.

Covariate balance was evaluated as the average absolute SMD of covariates after complete enrollment. The two-sided test of interest was whether average 12-month HbA1c was different in the intervention arm than control arm with alpha of 0.05. Under RBI, we estimated the power to reject the null hypothesis under each sharp treatment. We also considered estimator efficiency which was measured as the variance of the estimated mean difference in 12-month HbA1c across the 50K outcome datasets, and it was compared to the efficiency under CR. Under CR, a t-test could be an appropriate analyses. In this context, we quantified the gains in effective sample size to achieve the same amount of standard error efficiency as under CR. For power and efficiency comparisons, we also tested the difference of 12-month HbA1c using a regression model adjusting for covariates following CR. The pre-specified model mirrored the model under $D_{A-BCD}$ though with even more flexibility for continuous covariates by fitting restricted cubic splines with three knots each.

SMR(E, 20) achieved greater covariate balance, power, and efficiency than SMR(F, 20). For most matching schemes, it was generally true that estimating $F_b$ empirically was superior to estimating via $F_{p,n-p)}$. Full results are presented in figures for covariate-balance (Figure 3), power (Figure 4), and estimator efficiency (Figure 5).

When conditioning on all covariates, the average absolute SMD among covariates was 0.074 under SMR(E, 20) (Figure 3). Each extension improved upon overall covariate balance, with SRR(E, D), SRR(E, 20), SRR(F, 20), SRR(F, D), and MR improving covariate balance by a factor of at least 1.5-fold. Hence, we saw benefit of each extension individually and when combining SRR with a dynamic matching-threshold.

When conditioning on priority covariates, SMR(E, 20) achieved greater power to detect a treatment effect of -0.30 than many SMR schemes. Power further increased under SRR(F, D) on priority covariates, SRR(F, 20) on all covariates, SRR(E, D) on both sets of covariates, and MR. These same schemes and SMR(F, D) yielded more efficient estimators than SMR(E, 20) on priority covariates. SMR(E, 20) could have achieved the same standard error as CR with 145 fewer participants. Whereas, SRR(E, D) on priority covariates could have achieved the same CR standard error with 249 fewer participants. Again, we saw the benefit of SRR and batch randomization on improving power; SMR with a dynamic threshold nearly achieved the same power as SMR(E, 20). Each extension also improved estimator efficiency. SRR with a dynamic threshold achieved the greatest power and efficiency.

As a whole, matching schemes achieved greatest covariate-balance when adjusting for all covariates yet greatest power and estimator efficiency when adjusting for priority covariates. Three exceptions for increasing power were SRR(E, 20), SMR(E, D), and SRR(F, 20). The later two were also exceptions for increasing efficiency. Of these, SRR(F, 20) most
notably stood out. It was among the most powerful matching schemes when conditioning on all covariates and the least powerful scheme when conditioning on priority covariates – even less powerful than CR.

SRR, D_A-BCD, and PSR were each able to achieve greater power than CR followed by regression covariate-adjustment. D_A-BCD and PSR achieved greater power than alternative CAR schemes studied. When the treatment effect was strongest at -0.5, PSR achieved greater power than D_A-BCD; whereas, D_A-BCD achieved greater power than PSR for more moderate and mild treatment effects. PSR provided the most efficient randomization scheme. SRR(E, D) on priority covariates and PSR increased the relative efficiency by at least a factor 1.4.

6 Conclusions

This work accomplishes two major purposes: (1) it extends SMR methods to increase the covariate balance and inferential efficiency and (2) it provides a case study which motivates adjusting for covariates through randomization rather than through a comparable, flexible regression model.

SMR extensions include a mechanism for batch randomization, an allowance for matches to break and rematch (SRR), and a dynamic matching-threshold for finding mates. Sequential batch randomization and SRR were designed to recover some of the loss in covariate-balance and efficiency when using SMR as compared to MR. The dynamic matching-threshold was developed to address the challenge of pre-specifying an optimal matching-threshold prior to a trial. It reflects the chance of matching to a previously enrolled participant versus future enrollments and includes a mechanism to control the risk of chronological bias.

In simplified simulation settings, we found a fixed matching-threshold of 10-20% of the $F_{(p,n-p)}$ distribution to generally be a sweet spot matching-threshold for optimizing SMR covariate balance and estimator efficiency. Yet, the optimal fixed matching-threshold was sensitive to covariate distribution (categorical vs continuous), covariate association with outcome, and sample size. The presence of categorical covariates helped reduce the sensitivity to finding an optimal threshold. Still, using a dynamic matching-threshold with SMR achieved as good or better covariate-balance and estimator efficiency than using fixed thresholds. Except in a few instances, MR (the optimal setting for batch randomization) and SRR yielded superior covariate balance and efficiency than SMR. SMR with a dynamic matching-threshold yielded slightly better covariate balance and efficiency than SRR with a dynamic threshold. In these simplified settings we did not consider using a quantile of the empirically-estimated $F_{p,n}$, which could yield slightly different results and conclusions.

Benefits of each extension were also observed in a more complex, real-data application using the REACH trial (n = 512). After MR, SRR with a dynamic matching-threshold was the best sequential matching procedure for balancing baseline covariates, detecting a non-null treatment effect under RBI, and improving estimator efficiency. In almost all sequential matching schemes, performance was best when using a quantile from the empirically estimating the reference distribution of distances. We observed a balance / efficiency trade-off in choosing which covariates to adjust for in matched randomization schemes. Overall covariate balance was best when conditioning on all covariates of interest whereas power and efficiency were greatest when conditioning on priority covariates.

The REACH trial also highlighted the potential strengths of CAR. Unsurprisingly, CAR schemes achieved greater overall covariate balance than CR. Impressively, under RBI, SRR with a dynamic threshold, D_A-BCD, and PSR achieved greater power and efficiency than using CR and fitting a regression model adjusting for covariates. The pre-specified model included the same set of covariates and flexibly modelled continuous covariates using restricted cubic splines. It mirrored the model under D_A-BCD. In terms of covariate-balance and efficiency, stratified randomization on priority covariates was better than CR. Yet, it was inferior to aforementioned CAR strategies and deteriorated completely when adjusting for all covariates.

Among the side-by-side CAR comparisons, PSR yielded the most efficient estimator and was essentially tied with D_A-BCD for achieving the best covariate balance and power. The primary difference between PSR and matching methods is that PSR optimizes the overall Mahalanobis distance statistic whereas matching strategies optimizes the total sum of matched Mahalanobis distances. Unlike matching schemes studied, PSR and D_A-BCD universally performed better on our metrics of interest when conditioning on more covariates as compared to less.

This case study leads us to advocate for CAR under RBI as a robust and powerful strategy for testing intervention effects. We acknowledge that RBI has limitations. The foremost challenge may be to quickly implement the corresponding CAR algorithm at the time of enrollment, though some databases have this ability for at least some CAR schemes[24]. Some may also consider the randomization model to be limiting as compared to the population model (see [11] for an overview of randomization versus population model assumptions). Also, many CAR methods require a complete set of baseline covariates, to which we point to existing literature for a continued discussion for causal inference with missing
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data under RBI[25]. Though we do not tackle CAR missing data in depth here, we note that the nbpMatching package in R facilitated imputing temporary missing data while implementing SMR for randomization.

Figure 1: Average covariate balance (absolute Standardized Mean Difference) across 50K monte-carlo replicates. D on x-axis denotes performance under dynamic threshold. Covariates are distributed: CD1 – N(0, 1) and Bin(.2); CD2 – N(0, 1) and Bin(.5); and CD3 – N(0, 1) and N(0, 1).
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Figure 2: Estimator efficiency (standard deviation of estimates) across 50K monte-carlo replicates. Horizontal grey line highlights efficiency under CR whereas dashed lines are balance under single-batch MR. Predictiveness of each of the two covariates upon outcomes, in terms of $R^2$ are denoted as: CP1 – 25% each; CP2 – 10% and 25%; CP3 – 25% and 10%; and CP4 – 10% each.
Figure 3: Average balance across all baseline covariates of interest in REACH trial after CR, SMR, SMR, $D_A$-BCD, and PSR. Baseline SMR comparators are highlighted in orange and SMR extensions in purple. MR is considered an extension as an upper bound of gains possible through sequential batch randomization.
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Figure 4: Probability of rejecting the null hypothesis under sharp treatment effects ranging from 0 (null) to -0.5 (highly meaningful) in REACH trial under various randomization schemes. Power is calculated under randomization-based inference except for CR followed by ordinary least squares regression model (ANCOVA). The pre-specified regression model fit continuous covariates with splines to allow for non-linear associations with the outcome and closely mimicked the pre-specified model under D_{A-BCD}. The long-dash and short-dash lines are, respectively, the power of CR under RBI and under ANCOVA. Baseline SMR comparators are highlighted in orange and SMR extensions in purple. MR is considered an extension as an upper bound of gains possible through sequential batch randomization.
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Figure 5: Efficiency (variance of estimates) in estimating the difference in 12-month HbA1c between arms, relative to CR. Under CR, one could test with a t-test. Under this pretense, we provide the gains in effective sample size for each randomization scheme to achieve an equivalent standard error as under CR. Baseline SMR comparators are highlighted in orange and SMR extensions in purple. MR is considered an extension as an upper bound of gains possible through sequential batch randomization.

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6.2 Bibliography

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