Chapter 29
TMLE in Adaptive Group Sequential Covariate-Adjusted RCTs

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This chapter is devoted to group sequential covariate-adjusted RCTs analyzed through the prism of TMLE. By *adaptive covariate-adjusted design* we mean an RCT group sequential design that allows the investigator to dynamically modify its course through data-driven adjustment of the randomization probability based on data accrued so far, without negatively impacting the statistical integrity of the trial. Moreover, the patient's baseline covariates may be taken into account for the random treatment assignment. This definition is slightly adapted from Golub (2006). In particular, we assume following the definition of prespecified sampling plans given in Emerson (2006) that, prior to collection of the data, the trial protocol specifies the parameter of scientific interest, the inferential method, and confidence level to be used when constructing a confidence interval for the latter parameter.

Furthermore, we assume that the investigator specifies beforehand in the trial protocol a criterion of special interest that yields a notion of *optimal randomization scheme* that we therefore wish to target. For instance, the criterion could translate the necessity to minimize the number of patients assigned to their corresponding inferior treatment arm, subject to level and power constraints. Or the criterion could translate the necessity that a result be available as quickly as possible, subject to level and power constraints. The sole restriction on the criterion is that it must yield an optimal randomization scheme that can be approximated from the data accrued so far. The two examples above comply with this restriction.

We choose to consider specifically the second criterion cited above. Consequently, the optimal randomization scheme is the so-called *Neyman allocation*, which minimizes the asymptotic variance of the TMLE of the parameter of interest. We emphasize that there is nothing special about targeting the Neyman allocation, the whole methodology applying equally well to a large class of optimal randomization schemes derived from a variety of valid criteria.

By *adaptive group sequential design* we refer to the possibility of adjusting the randomization scheme only by blocks of c patients, where $c \geq 1$ is a prespecified integer (the case where $c = 1$ corresponds to a fully sequential adaptive design). The expression also refers to the fact that group sequential testing methods can be

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equally well applied on top of adaptive designs, an extension that we do not consider here. Although all our results (and their proofs) still hold for any $c \geq 1$, we consider the case $c = 1$ in the theoretical part of the chapter for simplicity's sake but the case where $c > 1$ is considered in the simulation study.

The literature on adaptive designs is vast, and our review is not comprehensive. The expression "adaptive design" has also been used in the literature for sequential testing and, in general, for designs that allow data-adaptive stopping times for the whole study (or for certain treatment arms) which achieve the desired type I and type II error requirements when testing a null hypothesis against its alternative. Data-adaptive randomization schemes go back to the 1930s, and we refer the interested reader to Hu and Rosenberger (2006, Sect. 1.2), Jennison and Turnbull (2000, Sect. 17.4), and Rosenberger (1996) for a comprehensive historical perspective.

Many articles have been devoted to the study of "response adaptive designs," an expression implicitly suggesting that those designs only depend on past responses of previous patients and not on the corresponding covariates. We refer readers to Hu and Rosenberger (2006) and Chambaz and van der Laan (2010) for a bibliography on that topic. On the contrary, covariate-adjusted response-adaptive (CARA) randomizations tackle the so-called issue of heterogeneity (i.e., the use of covariates in adaptive designs) by dynamically calculating the allocation probabilities on the basis of previous responses and current and past values of certain covariates. In this view, this chapter studies a new type of CARA procedure. The interest in CARA procedures is more recent, and there is a steadily growing number of articles dedicated to their study, starting with Rosenberger et al. (2001) and Bandyopadhyay and Biswas (2001), then Atkinson and Biswas (2005), Zhang et al. (2007), Zhang and Hu (2009), and Shao et al. (2010), among others. The latter articles are typically concerned with the convergence (almost sure and in law) of the allocation probabilities vector and of the estimator of the parameter *in a correctly specified parametric model*. The article by Shao et al. (2010) is devoted to the testing issue.

By contrast, the consistency and asymptotic normality results that we obtain here are robust to model misspecification. Thus, they notably contribute significantly to solving the question raised by the Food and Drug Administration (2006): *"When is it valid to modify randomization based on results, for example, in a combined phase 2/3 cancer trial?"* Finally, this chapter mainly relies on Chambaz and van der Laan (2010) and van der Laan (2008b), the latter technical report paving the way to robust and more efficient estimation based on adaptive RCTs in a variety of other setting (including the case that the outcome Y is a possibly censored time-to-event).

29.1 Statistical Framework

This chapter is devoted to the asymptotic study of *adaptive group sequential designs* in the case of RCTs with covariate, binary treatment and a one-dimensional primary outcome of interest. Thus, the experimental unit is $O = (W, A, Y)$, where $W \in \mathcal{W}$ consists of some baseline covariates, $A \in \mathcal{A} = \{0, 1\}$ denotes the assigned binary

treatment, and $Y \in \mathcal{Y}$ is the primary outcome of interest. For example, Y can indicate whether the treatment has been successful or not ($\mathcal{Y} = \{0, 1\}$), or Y can count the number of times an event of interest has occurred under the assigned treatment during a period of follow-up ($\mathcal{Y} = \mathbb{N}$), or Y can measure a quantity of interest after a given time has elapsed ($\mathcal{Y} = \mathbb{R}$). Although we will focus on the last case in this chapter, the methodology applies equally well to each example cited above.

Let us denote by P_0 the true distribution of the observed data structure O in the population of interest. We see P_0 as a specific element of the nonparametric set $\mathcal{M}$ of all possible observed data distributions. Note that, in order to avoid some technicalities, we assume (or rather impose) that all elements of $\mathcal{M}$ are dominated by a common measure. The parameter of scientific interest is the marginal effect of treatment $a = 1$ relative to treatment $a = 0$ on the additive scale, or risk difference: $\psi_0 = E_{P_0}[E_{P_0}(Y \mid A = 1, W) - E_{P_0}(Y \mid A = 0, W)]$. Of course, other choices such as the log-relative risk (the counterpart of the risk difference on the multiplicative scale) could be considered, and dealt with along the same lines. The risk difference can be interpreted causally under certain assumptions.

For all $P \in \mathcal{M}$, $Q_W(W; P) = P(W)$, $g(A \mid W; P) = P(A \mid W)$, and $Q_{Y|A,W}(O; P) = P(Y \mid A, W)$. We use the alternative notation $P = P_{Q,g}$ with $Q = Q(\cdot; P) \equiv (Q_W(\cdot; P), Q_{Y|A,W}(\cdot; P))$, and $g = g(\cdot \mid \cdot; P)$. Equivalently, $P_{Q,g}$ is the data-generating distribution such that $Q(\cdot; P_{Q,g}) = Q$ and $g(\cdot \mid \cdot; P_{Q,g}) = g$. In particular, we denote $Q_0 = Q(\cdot; P_0) = (Q_W(\cdot; P_0), Q_{Y|A,W}(\cdot; P_0))$. We also introduce the notation $\mathcal{Q} = \{Q(\cdot; P) : P \in \mathcal{M}\}$ for the nonparametric set of all possible values of Q, and $\mathcal{G} = \{g(\cdot \mid \cdot; P) : P \in \mathcal{M}\}$ for the nonparametric set of all possible values of g. Setting $\bar{Q}(A, W; P) = E_P(Y \mid A, W)$ and $\bar{Q}_0 = \bar{Q}(\cdot; P_0)$ [with a slight abuse, we also write sometimes $\bar{Q}(\cdot; Q)$ instead of $\bar{Q}(\cdot; P_{Q,g})$], we define in greater generality

$$\Psi(P) = E_P\left(\bar{Q}(1, W; P) - \bar{Q}(0, W; P)\right)$$

over the whole set $\mathcal{M}$, so that ψ_0 equivalently can be written as $\psi_0 = \Psi(P_0)$. This notation also emphasizes the fact that $\Psi(P)$ only depends on P through $\bar{Q}(\cdot; P)$ and $Q_W(\cdot; P)$, justifying the alternative notation $\Psi(P_{Q,g}) = \Psi(Q)$. The following proposition summarizes the most fundamental properties enjoyed by Ψ.

Proposition 29.1. *The functional Ψ is pathwise differentiable at every $P \in \mathcal{M}$. The efficient influence curve of Ψ at $P_{Q,g} \in \mathcal{M}$ is characterized by*

$$\begin{aligned} D^*(O; P_{Q,g}) &= D_1^*(W; Q) + D_2^*(O; P_{Q,g}), \text{ where} \\ D_1^*(W; Q) &= \bar{Q}(1, W) - \bar{Q}(0, W) - \Psi(Q), \text{ and} \\ D_2^*(O; P_{Q,g}) &= \frac{2A - 1}{g(A \mid W)}(Y - \bar{Q}(A, W)). \end{aligned}$$

The variance $\mathrm{var}_P D^*(O; P)^2$ *is the lower bound of the asymptotic variance of any regular estimator of $\Psi(P)$ in the i.i.d. setting. Furthermore, even if $Q \neq Q_0$,*

$$E_{P_0} D^*(O; P_{Q,g}) = 0 \quad \textit{implies} \quad \Psi(Q) = \Psi(Q_0) \tag{29.1}$$

when $g = g(\cdot \mid \cdot; P_0)$.

The implication (29.1) is the key to the robustness of the TMLE introduced and studied in this chapter. It is another justification of our interest in the pathwise differentiability of the functional Ψ and its efficient influence curve.

29.2 Data-Generating Mechanism

In order to formally describe the data-generating mechanism, we need to state a starting assumption. During the course of a clinical trial, it is possible to recruit independently the patients from a stationary population. In the counterfactual framework, this is equivalent to supposing that it is possible to sample as many independent copies of the full-data structure as required. Let us denote the ith observed data structure by $O_i = (W_i, A_i, Y_i)$. We also find it convenient to introduce $\mathbf{O}_n = (O_1, \ldots, O_n)$, and for every $i = 0, \ldots, n$, $\mathbf{O}_n(i) = (O_1, \ldots, O_i)$ [with the convention $\mathbf{O}(0) = \emptyset$].

By adjusting the randomization scheme as the data accrue, we mean that the nth treatment assignment A_n is drawn from $g_n(\cdot \mid W_n)$, where $g_n(\cdot \mid W)$ is a conditional distribution (or treatment mechanism) given the covariate W, which additionally depends on past observations $\mathbf{O}_{n-1}$. Since the sequence of treatment mechanisms cannot reasonably grow in complexity as the sample size increases, we will only consider data-adaptive treatment mechanisms such that $g_n(\cdot \mid W)$ depends on $\mathbf{O}_{n-1}$ only through a finite-dimensional summary measure $Z_n = \phi_n(\mathbf{O}_{n-1})$, where the measurable function ϕ_n maps $\mathcal{O}^{n-1}$ onto $\mathbb{R}^d$ (where $\mathcal{O}$ is the set from which O takes its values) for some fixed $d \geq 0$ [$d = 0$ corresponds to the case where $g_n(\cdot \mid W)$ actually does not adapt]. For instance, $Z_{n+1} = \phi_{n+1}(\mathbf{O}_n) \equiv (n^{-1} \sum_{i=1}^n Y_i I(A_i = 0), n^{-1} \sum_{i=1}^n Y_i I(A_i = 1))$ characterizes a proper summary measure of the past, which keeps track of the mean outcome in each treatment arm. Another sequence of mappings ϕ_n will be at the core of the adaptive methodology that we study in depth in this chapter, see (29.4).

Formally, the data-generating mechanism is specified by the following factorization of the likelihood of $\mathbf{O}_n$:

$$\prod_{i=1}^n (Q_W(W_i; P_0) \times Q_{Y|A,W}(O_i; P_0)) \times \prod_{i=1}^n g_i(A_i \mid W_i),$$

which suggests the introduction of $\mathbf{g}_n = (g_1, \ldots, g_n)$, referred to as the *design of the study*, and the expression "$\mathbf{O}_n$ is drawn from $(Q_0, \mathbf{g}_n)$." Likewise, the likelihood of $\mathbf{O}_n$ under $(Q, \mathbf{g}_n)$ [where $Q = (Q_W, Q_{Y|A,W}) \in \mathcal{Q}$ is a candidate value for Q_0] is

$$\prod_{i=1}^n (Q_W(W_i) \times Q_{Y|A,W}(O_i)) \times \prod_{i=1}^n g_i(A_i \mid W_i),$$

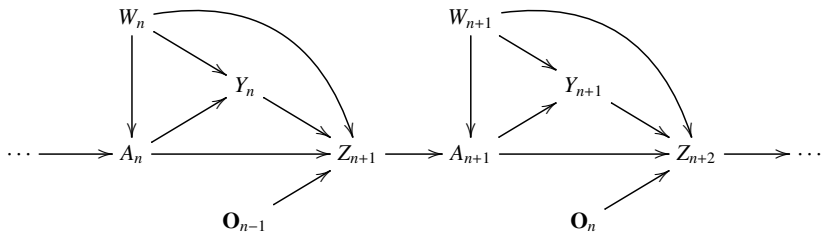

Fig. 29.1 A possible causal graph describing the data-generating mechanism

where we emphasize that the second factor is known. Thus we will refer with a slight abuse of terminology to $\sum_{i=1}^{n} \log Q_W(W_i) + \log Q_{Y|A,W}(O_i)$ as the log-likelihood of $\mathbf{O}_n$ under $(Q, \mathbf{g}_n)$. Furthermore, given $\mathbf{g}_n$, we introduce the notation $P_{Q_0,g_i} f \equiv E_{P_{Q_0,g_i}}(f(O_i) \mid \mathbf{O}_n(i-1))$ for any possibly vector-valued measurable f defined on $\mathcal{O}$.

Another equivalent characterization of the data-generating mechanism involves the causal graph shown in Fig. 29.1. It is seen again that W_n is drawn independently from the past $\mathbf{O}_{n-1}$. Secondly, A_n is a deterministic function of W_n, the summary measure Z_n (which depends on $\mathbf{O}_{n-1}$), and a new independent source of randomness [in other words, it is drawn conditionally on (W_n, Z_n) and conditionally independently of the past $\mathbf{O}_{n-1}$]. Thirdly, Y_n is a deterministic function of (A_n, W_n) and a new independent source of randomness [it is drawn conditionally on (A_n, W_n) and conditionally independently of the past $\mathbf{O}_{n-1}$]. Then the next summary measure Z_{n+1} is obtained as a function of $\mathbf{O}_{n-1}$ and $O_n = (W_n, A_n, Y_n)$, and so on.

Finally, it is interesting in practice to adapt the design group sequentially. This can be simply formalized. For a given prespecified integer $c \geq 1$ ($c = 1$ corresponds to a fully sequential adaptive design), going forward c-group sequentially simply amounts to imposing $\phi_{(r-1)c+1}(\mathbf{O}_{(r-1)c}) = \ldots = \phi_{rc}(\mathbf{O}_{rc-1})$ for all $r \geq 1$. Then the c treatment assignments $A_{(r-1)c+1}, \ldots, A_{rc}$ in the rth c-group are all drawn from the same conditional distribution $g_{(r-1)c}(\cdot \mid W)$. Yet, although all our results (and their proofs) still hold for any $c \geq 1$, we prefer to consider in the rest of this section and in Sects. 29.4 and 29.5 the case where $c = 1$ for simplicity's sake. In contrast, the simulation study carried out in Sect. 29.6 involves some $c > 1$.

29.3 Optimal Design

One of the most important features of the adaptive group sequential design methodology is that it *targets* a *user-supplied* specific design of special interest. This specific design is generally an optimal design with respect to a criterion that translates what the investigator is most concerned about. Specifically, one could be most concerned with the well-being of the target population, wishing that a result be available

as quickly as possible and aspiring therefore to the highest efficiency (i.e., the ability to reach a conclusion as quickly as possible subject to level and power constraints). Or one could be most concerned with the well-being of the subjects participating in the clinical trial, therefore trying to minimize the number of patients assigned to their corresponding inferior treatment arms, subject to level and power constraints. Obviously, these are only two important examples from a large class of potentially interesting criteria. The sole purpose of the criterion is to generate a random element in $\mathcal{G}$ of the form $g_n = g_{Z_n}$, where $Z_n = \phi_n(\mathbf{O}_{n-1})$ is a finite-dimensional summary measure of $\mathbf{O}_{n-1}$, and g_n converges to a desired or optimal fixed treatment mechanism. We decide to focus in this chapter on the first example, but it must be clear that the methodology applies to a variety of other criteria. See van der Laan (2008b) for other examples.

By Proposition 29.1, the asymptotic variance of any regular estimator of the risk difference $\Psi(Q_0)$ has lower bound $\mathrm{var}_{P_{Q_0,g}} D^*(O; P_{Q_0,g})$ if the estimator relies on data sampled independently from $P_{Q_0,g}$. We have that

$$\begin{aligned}\mathrm{var}_{P_{Q_0,g}} D^*(O; P_{Q_0,g}) = {} & E_{Q_0}(\bar{Q}_0(1, W) - \bar{Q}_0(0, W) - \Psi(Q_0))^2 \\ & + E_{Q_0}\left(\frac{\sigma^2(Q_0)(1, W)}{g(1 \mid W)} + \frac{\sigma^2(Q_0)(0, W)}{g(0 \mid W)}\right),\end{aligned}$$

where $\sigma^2(Q_0)(A, W)$ denotes the conditional variance of Y given (A, W) under Q_0. We use the notation E_{Q_0} above (for the expectation with respect to the marginal distribution of W under P_0) in order to emphasize the fact that the treatment mechanism g only appears in the second term of the right-hand side sum. Furthermore, it holds P_0–almost surely that

$$\frac{\sigma^2(Q_0)(1, W)}{g(1 \mid W)} + \frac{\sigma^2(Q_0)(0, W)}{g(0 \mid W)} \geq (\sigma(Q_0)(1, W) + \sigma(Q_0)(0, W))^2,$$

with equality if and only if

$$g(1 \mid W) = \frac{\sigma(Q_0)(1, W)}{\sigma(Q_0)(1, W) + \sigma(Q_0)(0, W)}, \tag{29.2}$$

P_0–almost surely. Therefore, the following lower bound holds for all $g \in \mathcal{G}$:

$$\begin{aligned}\mathrm{var}_{P_{Q_0,g}} D^*(O; P_{Q_0,g}) \geq {} & E_{Q_0}(\bar{Q}_0(1, W) - \bar{Q}_0(0, W) - \Psi(Q_0))^2 \\ & + E_{Q_0}(\sigma(Q_0)(1, W) + \sigma(Q_0)(0, W))^2,\end{aligned}$$

with equality if and only if $g \in \mathcal{G}$ is characterized by (29.2). This optimal design is known in the literature as the *Neyman allocation* (Hu and Rosenberger 2006, p. 13). This result makes clear that the most efficient treatment mechanism assigns with higher probability a patient with covariate vector W to the treatment arm with the largest variance of the outcome Y, regardless of the mean of the outcome (i.e., whether the arm is inferior or superior).

Due to logistical reasons, it might be preferable to consider only treatment mechanisms that assign treatment in response to a subvector V of the baseline covariate vector W. In addition, if W is complex, targeting the optimal Neyman allocation might be too ambitious. Therefore, we will consider the important case where V is a discrete covariate with finitely many values in the set $\mathcal{V} = \{1, \ldots, \nu\}$. The covariate V indicates subgroup membership for a collection of ν subgroups of interest. We decide to restrict the search for an optimal design to the set $\mathcal{G}_1 \subset \mathcal{G}$ of those treatment mechanisms that only depend on W through V. The same calculations as above yield straightforwardly that, for all $g \in \mathcal{G}_1$

$$\begin{aligned}\mathrm{var}_{P_{Q_0,g}} D^*(O; P_{Q_0,g}) \geq E_{Q_0}(\bar{Q}_0(1, W) - \bar{Q}_0(0, W) - \Psi(Q_0))^2 \\ + E_{Q_0}(\bar{\sigma}(Q_0)(1, V) + \bar{\sigma}(Q_0)(0, V))^2,\end{aligned}$$

where $\bar{\sigma}^2(Q_0)(a, V) = E_{Q_0}(\sigma^2(Q_0)(a, W) \mid V)$ for $a \in \mathcal{A}$, with equality if and only if g coincides with $g^*(Q_0)$, characterized by

$$g^*(Q_0)(1|V) = \frac{\bar{\sigma}(Q_0)(1, V)}{\bar{\sigma}(Q_0)(1, V) + \bar{\sigma}(Q_0)(0, V)},$$

P_0–almost surely. Hereafter, we refer to $g^*(Q_0)$ as *the optimal design*.

Because $g^*(Q_0)$ is characterized as the minimizer over $g \in \mathcal{G}_1$ of the variance under $P_{Q_0,g}$ of the efficient influence curve at $P_{Q_0,g}$, we propose to construct $g_{n+1} \in \mathcal{G}_1$ as the minimizer over $g \in \mathcal{G}_1$ of an estimator of the latter variance based on past observations $\mathbf{O}_n$. We proceed by recursion. We first set $g_1 = g^b$, the so-called balanced treatment mechanism such that $g^b(1 \mid W) = 1/2$ for all $W \in \mathcal{W}$, and assume that $\mathbf{O}_n$ has already been sampled from $(Q_0, \mathbf{g}_n)$, the sample size being large enough to guarantee $\sum_{i=1}^n I(V_i = v) > 0$ for all $v \in \mathcal{V}$ (if n_0 is the smallest sample size such that the previous condition is met, then we set $g_1 = \ldots = g_{n_0} = g^b$).

The issue is now to construct g_{n+1}. Let us assume for the time being that we already know how to construct an estimator Q_n of Q_0 based on $\mathbf{O}_n$ [hence the estimators $\bar{Q}_n = \bar{Q}(\cdot; Q_n)$ of $\bar{Q}_0$ and $\Psi(Q_n)$ of $\Psi(Q_0) = \psi_0$]. The reasoning is not circular by virtue of the chronological ordering as it is summarized in Fig. 29.1, for instance. Then, for all $g \in \mathcal{G}_1$,

$$\begin{aligned}S_n(g) &= \frac{1}{n}\sum_{i=1}^n \left(D_1^*(W_i; Q_n)^2 + 2D_1^*(W_i; Q_n) D_2^*(O_i; P_{Q_n,g}) \frac{g(A_i \mid V_i)}{g_i(A_i \mid V_i)} \right. \\ &\quad \left. + D_2^*(O_i; P_{Q_n,g})^2 \frac{g(A_i \mid V_i)}{g_i(A_i \mid V_i)} \right) \\ &\quad - \left(\frac{1}{n}\sum_{i=1}^n D_1^*(W_i; Q_n) + D_2^*(O_i; P_{Q_n,g}) \frac{g(A_i \mid V_i)}{g_i(A_i \mid V_i)} \right)^2 \\ &= \frac{1}{n}\sum_{i=1}^n \frac{(Y_i - \bar{Q}_n(A_i, W_i))^2}{g(A_i|V_i) g_i(A_i|V_i)}\end{aligned}$$

$$+\left\{\frac{1}{n}\sum_{i=1}^{n} D_1^*(W_i;Q_n)^2 + 2D_1^*(W_i;Q_n)D_2^*(O_i;P_{Q_n,g_i}) - \left(\frac{1}{n}\sum_{i=1}^{n} D_1^*(W_i;Q_n) + D_2^*(O_i;P_{Q_n,g_i})\right)^2\right\}$$

estimates $\mathrm{var}_{P_{Q_0,g}} D^*(O;P_{Q_0,g})$ (the weighting provides the adequate tilt of the empirical distribution; it is not necessary to weight the terms corresponding to D_1^* because they do not depend on the treatment mechanism). Now, only the first term in the rightmost expression still depends on g. The same calculation as above straightforwardly yields that $S_n(g)$ is minimized at $g_{n+1} \in \mathcal{G}_1$ characterized by

$$g_{n+1}(1 \mid v) = \frac{s_{v,n}(1)}{s_{v,n}(1) + s_{v,n}(0)}$$

for all $v \in \mathcal{V}$, where for each $(v,a) \in \mathcal{V} \times \mathcal{A}$

$$s_{v,n}^2(a) = \frac{\frac{1}{n}\sum_{i=1}^{n} \frac{(Y_i - \bar{Q}_n(A_i,W_i))^2}{g_i(A_i|V_i)} I((V_i,A_i) = (v,a))}{\frac{1}{n}\sum_{i=1}^{n} I(V_i = v)}.$$

Yet, instead of considering the above characterization, we find it more convenient to define

$$g_{n+1}^*(1 \mid v) = \frac{\sigma_{v,n}(1)}{\sigma_{v,n}(1) + \sigma_{v,n}(0)}, \tag{29.3}$$

for all $v \in \mathcal{V}$, where for each $(v,a) \in \mathcal{V} \times \mathcal{A}$

$$\sigma_{v,n}^2(a) = \frac{\frac{1}{n}\sum_{i=1}^{n} \frac{(Y_i - \bar{Q}_n(A_i,W_i))^2}{g_i(A_i|V_i)} I((V_i,A_i) = (v,a))}{\frac{1}{n}\sum_{i=1}^{n} \frac{I((V_i,A_i)=(v,a))}{g_i(a|v)}}.$$

Note that $s_{v,n}^2(a)$ and $\sigma_{v,n}^2(a)$ share the same numerator, and that the different denominators converge to the same limit. Substituting $\sigma_{v,n}^2(a)$ for $s_{v,n}^2(a)$ is convenient because one naturally interprets the former as an estimator of the conditional variance of Y given $(A,V) = (a,v)$ based on $\mathbf{O}_n$, a fact that we use in Sect. 29.4.2. Finally, we emphasize that $g_{n+1}^* = g_{Z_{n+1}}$ for the summary measure of the past $\mathbf{O}_n$

$$Z_{n+1} = \phi_{n+1}(\mathbf{O}_n) \equiv ((\sigma_{v,n}^2(0), \sigma_{v,n}^2(1)) : v \in \mathcal{V}). \tag{29.4}$$

The rigorous definition of the design $\mathbf{g}_n^* = (g_1^*, \ldots, g_n^*)$ follows by recursion, but it is still subject to knowledge about how to construct an estimator Q_n of Q_0 based on $\mathbf{O}_n$. Because this last missing piece of the formal definition of the adaptive group sequential design data-generating mechanism is also the core of the TMLE procedure, we address it in Sect. 29.4.

29.4 TMLE Procedure

We assume hereafter that $\mathbf{O}_n$ has already been sampled from the $(Q_0, \mathbf{g}_n^*)$-adaptive sampling scheme. In this section, we construct an estimator Q_n (actually denoted by Q_n^*) of Q_0, thereby yielding the characterization of g_{n+1}^* and completing the formal definition of the adaptive design $\mathbf{g}_n^*$. In particular, the next data structure O_{n+1} can be drawn from (Q_0, g_{n+1}^*), and it makes sense to undertake the asymptotic study of the properties of the TMLE methodology based on adaptive group sequential sampling. As in the i.i.d. framework, the TMLE procedure maps an initial substitution estimator $\Psi(Q_n^0)$ of ψ_0 into an update $\psi_n^* = \Psi(Q_n^*)$ by fluctuating the initial estimate Q_n^0 of Q_0.

29.4.1 Initial ML-Based Substitution Estimator

The working model. In order to construct the initial estimate Q_n^0 of Q_0, we consider a *working model* $\mathcal{Q}_n^w$. With a slight abuse of notation, the elements of $\mathcal{Q}_n^w$ are denoted by $(Q_W(\cdot; P_n), Q_{Y|A,W}(\cdot; \theta))$ for some parameter $\theta \in \Theta$, where $Q_W(\cdot; P_n)$ is the empirical marginal distribution of W. Specifically, the working model $\mathcal{Q}_n^w$ is chosen in such a way that

$$Q_{Y|A,W}(O;\theta) = \frac{1}{\sqrt{2\pi\sigma_V^2(A)}} \exp\left\{-\frac{(Y - m(A,W;\beta_V))^2}{2\sigma_V^2(A)}\right\}.$$

This implies that for any $P_\theta \in \mathcal{M}$ such that $Q_{Y|A,W}(\cdot; P_\theta) = Q_{Y|A,W}(\cdot;\theta)$, the conditional mean $\bar{Q}(A, W; P_\theta)$, which we also denote by $\bar{Q}(A, W;\theta)$, satisfies $\bar{Q}(A, W;\theta) = m(A, W;\beta_V)$, the right-hand side expression being a linear combination of variables extracted from (A, W) and indexed by the regression vector β_V (of dimension b). Defining

$$\theta(v) = (\beta_v, \sigma_v^2(0), \sigma_v^2(1))^\top \in \Theta_v \subset \mathbb{R}^b \times \mathbb{R}_+^* \times \mathbb{R}_+^* \tag{29.5}$$

for each $v \in \mathcal{V}$, the complete parameter is given by $\theta = (\theta(1)^\top, \ldots, \theta(v)^\top)^\top \in \Theta$, where $\Theta = \prod_{v=1}^{v} \Theta_v$. We impose the following conditions on the parameterization: The parameter set Θ is compact. Furthermore, the linear parameterization is identifiable; for all $v \in \mathcal{V}$, if $m(a, w;\beta_v) = m(a, w;\beta_v')$ for all $a \in \mathcal{A}$ and $w \in \mathcal{W}$ (compatible with v), then necessarily $\beta_v = \beta_v'$.

Characterizing Q_n^0. Let us set a reference fixed design $g^r \in \mathcal{G}_1$. We now characterize Q_n^0 by letting $Q_n^0 = (Q_W(\cdot; P_n), Q_{Y|A,W}(\cdot;\theta_n))$, where

$$\theta_n = \arg\max_{\theta\in\Theta} \sum_{i=1}^{n} \log Q_{Y|A,W}(O_i;\theta) \frac{g^r(A_i \mid V_i)}{g_i^*(A_i \mid V_i)} \tag{29.6}$$

is a *weighted* maximum likelihood estimator with respect to the working model. Thus, the vth component $\theta_n(v)$ of θ_n satisfies

$$\theta_n(v) = \arg\min_{\theta(v)\in\Theta_v} \sum_{i=1}^{n} \left(\log \sigma_v^2(A_i) + \frac{(Y_i - m(A_i, W_i; \beta_v))^2}{\sigma_v^2(A_i)} \right) \frac{g^r(A_i \mid V_i)}{g_i^*(A_i \mid V_i)} I(V_i = v)$$

for every $v \in \mathcal{V}$. Note that this initial estimate Q_n^0 of Q_0 yields the initial maximum-likelihood-based substitution estimator $\Psi(Q_n^0)$ of ψ_0:

$$\Psi(Q_n^0) = \frac{1}{n} \sum_{i=1}^{n} \bar{Q}(1, W_i; \theta_n) - \bar{Q}(0, W_i; \theta_n).$$

Studying Q_n^0 through θ_n. For simplicity, let us introduce, for all $\theta \in \Theta$, the additional notation: $\ell_{\theta,0} = \log Q_{Y|A,W}(\cdot;\theta)$, $\dot{\ell}_{\theta,0} = \frac{\partial}{\partial\theta}\ell_{\theta,0}$, and $\ddot{\ell}_{\theta,0} = \frac{\partial^2}{\partial\theta^2}\ell_{\theta,0}$. The first asymptotic property of θ_n that we derive concerns its consistency (see Theorem 5 in van der Laan 2008b).

Proposition 29.2. *Assume that*

A1. *There exists a unique interior point $\theta_0 \in \Theta$ such that*

$$\theta_0 = \arg\max_{\theta\in\Theta} P_{Q_0,g^r}\ell_{\theta,0};$$

A2. *The matrix $-P_{Q_0,g^r}\ddot{\ell}_{\theta_0,0}$ is positive definite.*

Provided that $\mathcal{O}$ is a bounded set, θ_n consistently estimates θ_0.

The limit in probability of θ_n has a nice interpretation in terms of projection of $Q_{Y|A,W}(\cdot; P_0)$ onto $\{Q_{Y|A,W}(\cdot;\theta) : \theta \in \Theta\}$. Preferring to discuss this issue in terms of the data-generating distribution rather than conditional distribution, let us set $Q_{\theta_0} = (Q_W(\cdot; P_0), Q_{Y|A,W}(\cdot;\theta_0))$ and assume that $P_{Q_0,g^r} \log Q_{Y|A,W}(\cdot; P_0)$ is well defined (this weak assumption concerns Q_0, not g^r, and holds for instance when $|\log Q_{Y|A,W}(\cdot; P_0)|$ is bounded). Then A1 is equivalent to $P_{Q_{\theta_0},g^r}$ being the unique Kullback–Leibler projection of P_{Q_0,g^r} onto the set

$$\{P \in \mathcal{M} : \exists\, \theta \in \Theta \text{ s.t. } Q_{Y|A,W}(\cdot; P) = Q_{Y|A,W}(\cdot;\theta), \text{ and } Q_W(\cdot; P) = Q_W(\cdot; P_0), g(\cdot \mid \cdot; P) = g^r\}.$$

In addition to being consistent, θ_n actually satisfies a central limit theorem if supplementary mild conditions are met. The latter central limit theorem is embedded in a more general result that we state in Sect. 29.4.3; see Proposition 29.5.

The cornerstone of the proof of Proposition 29.2 is to interpret θ_n as the solution in θ of the martingale estimating equation $\sum_{i=1}^{n} D_1(\theta)(O_i, Z_i) = 0$, where Z_i is the finite-dimensional summary measure of past observation $\mathbf{O}_n(i-1)$ such that g_i^* depends on $\mathbf{O}_n(i-1)$ only through Z_i (hence the notation $g_i^* = g_{Z_i}$) and $D_1(\theta)(O, Z) = \dot{\ell}_{\theta,0}(O) g^r(A \mid V)/g_Z(A \mid V)$ satisfies $P_{Q_0,g_i^*} D_1(\theta_0) = 0$ for all $i \le n$.

By relying on a Kolmogorov strong law of large numbers for martingales (see Theorem 8 in Chambaz and van der Laan 2010), one obtains that $n^{-1}\sum_{i=1}^{n} P_{Q_0,g_i^*} D_1(\theta_n)$ converges to zero almost surely. This results in the convergence in probability of θ_n to θ_0 by a Taylor expansion of $\theta \mapsto P_{Q_0,g^r}\dot{\ell}_{\theta,0}$ at θ_0 (hence assumption A2). The strong law of large numbers applies because the geometry of $\mathcal{F} = \{D_1(\theta) : \theta \in \Theta\}$ is moderately complex [heuristically, $\mathcal{F}$ can be covered by finitely many $\|\cdot\|_\infty$-balls because Θ is a compact set, (O, Z) is bounded, and the mapping $(o, z, \theta) \mapsto D_1(\theta)(o, z)$ is continuous; and the number of such balls of radius η needed to cover $\mathcal{F}$ does not grow too fast as η goes to zero].

Furthermore, maximizing a weighted version of the log-likelihood is a technical twist that makes the theoretical study of the properties of θ_n easier. Indeed, the unweighted maximum likelihood estimator $t_n = \arg\max_{\theta\in\Theta}\sum_{i=1}^{n}\log Q_{Y|A,W}(O_i;\theta)$ targets the parameter

$$T_{\bar{g}_n}(Q_0) = \arg\max_{\theta\in\Theta}\sum_{i=1}^{n} P_{Q_0,g_i^*}\log Q_{Y|A,W}(O_i;\theta) = \arg\max_{\theta\in\Theta} P_{Q_0,\bar{g}_n}\ell_{\theta,0},$$

where $\bar{g}_n = \frac{1}{n}\sum_{i=1}^{n} g_i^*$. Therefore, t_n asymptotically targets the limit, if it exists, of $T_{\bar{g}_n}(Q_0)$. Assuming that $\bar{g}_n$ converges itself to a fixed design $g_\infty \in \mathcal{G}$, then t_n asymptotically targets parameter $T_{g_\infty}(Q_0)$. The latter parameter is very difficult to interpret and to analyze as it depends directly and indirectly (through g_∞) on Q_0.

29.4.2 Convergence of the Adaptive Design

Consider the mapping G^* from Θ to $\mathcal{G}_1$ [respectively equipped with the Euclidean distance and, for instance, the distance $d(g, g') = \sum_{v\in\mathcal{V}}|g(1 \mid v) - g'(1 \mid v)|$] such that, for any $\theta \in \Theta$, for any $(a, v) \in \mathcal{A}\times\mathcal{V}$

$$G^*(\theta)(a \mid v) = \frac{\sigma_v(a)}{\sigma_v(1) + \sigma_v(0)}. \tag{29.7}$$

Equation (29.7) characterizes G^*, which is obviously continuous. Since $\mathbf{g}_n^*$ is adapted in such a way that $g_n^* = G^*(\theta_n)$, Proposition 29.2 and the continuous mapping theorem (see Theorem 1.3.6 in van der Vaart and Wellner 1996) straightforwardly imply the following result.

Proposition 29.3. *Under the assumptions of Proposition 29.2, the adaptive design* $\mathbf{g}_n^*$ *converges in probability to the limit design* $G^*(\theta_0)$.

The convergence of the adaptive design $\mathbf{g}_n^*$ is a crucial result. It is noteworthy that the limit design $G^*(\theta_0)$ equals the optimal design $g^*(Q_0)$ if the working model is correctly specified (which never happens in practical applications), but not necessarily otherwise. Furthermore, the relationship $g_n^* = G^*(\theta_n)$ also entails the possibility of deriving the convergence in distribution of $\sqrt{n}(g_n^* - G^*(\theta_0))$ to a centered Gaussian

distribution with known variance by application of the delta method (G^* is differentiable) from a central limit theorem on θ_n (Proposition 29.5).

29.4.3 The TMLE

Fluctuating Q_n^0. The second step of the TMLE procedure stretches the initial estimate $\Psi(Q_n^0)$ in the direction of the parameter of interest, through a maximum likelihood step over a well-chosen fluctuation of Q_n^0. The latter fluctuation of Q_n^0 is just a one-dimensional parametric model $\{Q_n^0(\epsilon) : \epsilon \in \mathcal{E}\} \subset \mathcal{Q}$ indexed by the parameter $\epsilon \in \mathcal{E}$, $\mathcal{E} \subset \mathbb{R}$ being a bounded interval that contains a neighborhood of the origin. Specifically, we set, for all $\epsilon \in \mathcal{E}$, $Q_n^0(\epsilon) = (Q_W(\cdot; P_n), Q_{Y|A,W}(\cdot; \theta_n, \epsilon))$, where for any $\theta \in \Theta$:

$$Q_{Y|A,W}(O; \theta, \epsilon) = \frac{1}{\sqrt{2\pi\sigma_V^2(A)}} \exp\left\{-\frac{(Y - \bar{Q}(A, W; \theta) - \epsilon H^*(A, W; \theta))^2}{2\sigma_V^2(A)}\right\}, \quad (29.8)$$

with

$$H^*(A, W; \theta) = \frac{2A - 1}{G^*(\theta)(A \mid V)}\sigma_V^2(A).$$

In particular, the fluctuation goes through Q_n^0 at $\epsilon = 0$ (i.e., $Q_n^0(0) = Q_n^0$). Let $P_n^0(\epsilon) \in \mathcal{M}$ be a data-generating distribution such that $Q_{Y|A,W}(\cdot; P_n^0(\epsilon)) = Q_{Y|A,W}(\cdot; \theta_n, \epsilon)$. The conditional mean $\bar{Q}(A, W; P_n^0(\epsilon))$, which we also denote by $\bar{Q}(A, W; \theta_n, \epsilon)$, is $\bar{Q}(A, W; \theta_n, \epsilon) = \bar{Q}(A, W; \theta_n) + \epsilon H^*(A, W; \theta_n)$. Furthermore, the score at $\epsilon = 0$ of $P_n^0(\epsilon)$ equals

$$\frac{\partial}{\partial\epsilon} \log P_n^0(\epsilon)(O)\Big|_{\epsilon=0} = \frac{2A - 1}{G^*(\theta_n)(A \mid V)}(Y - \bar{Q}(A, W; \theta_n)) = D_2^*(O; P_{Q_n^0, G^*(\theta_n)}),$$

the second component of the efficient influence curve of Ψ at $P_{Q_n^0, G^*(\theta_n)} = P_{Q_n^0, g_n^*}$. Recall that $g_n^* = G^*(\theta_n)$.

Characterizing the TMLE Q_n^*. We characterize the update Q_n^* of Q_n^0 in the fluctuation $\{Q_n^0(\epsilon) : \epsilon \in \mathcal{E}\}$ by $Q_n^* = Q_n^0(\epsilon_n)$, where

$$\epsilon_n = \arg\max_{\epsilon \in \mathcal{E}} \sum_{i=1}^n \log Q_{Y|A,W}(O_i; \theta_n, \epsilon) \frac{g_n^*(A_i \mid V_i)}{g_i^*(A_i \mid V_i)} \quad (29.9)$$

is a *weighted* maximum likelihood estimator with respect to the fluctuation. It is worth noting that ϵ_n is known in closed form (we assume, without serious loss of generality, that $\mathcal{E}$ is large enough for the maximum to be achieved in its interior). Denoting the vth component $\theta_n(v)$ of θ_n by $(\beta_{v,n}, \sigma_{v,n}^2(0), \sigma_{v,n}^2(1))^\top$, it holds that

$$\epsilon_n = \frac{\sum_{i=1}^n (Y_i - \bar{Q}(A_i, W_i; \theta_n)) \frac{2A_i - 1}{g_i^*(A_i|V_i)}}{\sum_{i=1}^n \frac{\sigma^2_{V_i,n}(A_i)}{g_n^*(A_i|V_i) g_i(A_i|V_i)}}.$$

The notation Q_n^* for this first update of Q_n^0 is a reference to the fact that the TMLE procedure, which is in greater generality an iterative procedure, converges here in one single step. Indeed, suppose that one fluctuates Q_n^* as we fluctuate Q_n^0 i.e., by introducing $Q_n^1(\epsilon) = (Q_W(\cdot; P_n), Q_{Y|A,W}(\cdot; \theta_n, \epsilon_n, \epsilon))$ with $Q_{Y|A,W}(O; \theta, \epsilon', \epsilon)$ equal to the right-hand side of (29.8), where one substitutes $\bar{Q}(A, W; \theta, \epsilon')$ for $\bar{Q}(A, W; \theta)$. In addition, suppose that one then defines the weighted maximum likelihood ϵ_n' as the right-hand side of (29.9), where one substitutes $Q_{Y|A,W}(O_i; \theta_n, \epsilon_n, \epsilon)$ for $Q_{Y|A,W}(O_i; \theta_n, \epsilon)$. Then it follows that $\epsilon_n' = 0$ so that the "updated" $Q_n^*(\epsilon_n') = Q_n^*$. The updated estimator Q_n^* of Q_0 maps into the TMLE $\psi_n^* = \Psi(Q_n^*)$ of the risk difference $\psi_0 = \Psi(Q_0)$:

$$\psi_n^* = \frac{1}{n} \sum_{i=1}^n \bar{Q}(1, W_i; \theta_n, \epsilon_n) - \bar{Q}(0, W_i; \theta_n, \epsilon_n). \tag{29.10}$$

The asymptotics of ψ_n^* relies on a central limit theorem for (θ_n, ϵ_n), which we discuss in Sect. 29.5.

29.5 Asymptotics

We now state and comment on a consistency result for the stacked estimator (θ_n, ϵ_n), which complements Proposition 29.2 (see Theorem 8 in van der Laan 2008b). For simplicity, let us generalize the notation $\ell_{\theta,0}$ introduced in Sect. 29.4.1 by setting, for all $(\theta, \epsilon) \in \Theta \times \mathcal{E}$,$\ell_{\theta,\epsilon} = \log Q_{Y|A,W}(\cdot; \theta, \epsilon)$. Moreover, let us set, for all $(\theta, \epsilon) \in \Theta \times \mathcal{E}$: $Q_{\theta,\epsilon} = (Q_W(\cdot; P_0), Q_{Y|A,W}(\cdot; \theta, \epsilon))$.

Proposition 29.4. *Suppose that assumptions A1 and A2 from Proposition 29.2 hold. In addition, assume that:*

A3. *There exists a unique interior point $\epsilon_0 \in \mathcal{E}$ such that*

$$\epsilon_0 = \arg\max_{\epsilon \in \mathcal{E}} P_{Q_0, G^*(\theta_0)} \ell_{\theta_0, \epsilon}.$$

(1) It holds that $\Psi(Q_{\theta_0,\epsilon_0}) = \Psi(Q_0)$;
(2) Provided that O is a bounded set, (θ_n, ϵ_n) consistently estimates (θ_0, ϵ_0).

We already discussed the interpretation of the almost sure limit of θ_n in terms of the Kullback-Leibler projection. Likewise, the almost sure limit ϵ_0 of ϵ_n enjoys such an interpretation. Let us assume that $P_{Q_0,G^*(\theta_0)} \log Q_{Y|A,W}(\cdot; P_0)$ is well defined [this weak assumption concerns Q_0, not $G^*(\theta_0)$, and holds for instance when $|\log Q_{Y|A,W}(\cdot; P_0)|$ is bounded]. Then A3 is equivalent to $P_{Q_{\theta_0,\epsilon_0},G^*(\theta_0)}$ being

the unique the Kullback–Leibler projection of $P_{Q_0,G^*(\theta_0)}$ onto the set $\{P \in \mathcal{M} : \exists \epsilon \in \mathcal{E} \text{ s.t. } Q(\cdot; P) = Q_{\theta_0,\epsilon} \text{ and } g(\cdot \mid \cdot; P) = G^*(\theta_0)\}$.

Of course, the most striking property that ϵ_0 enjoys is (1): Even if $\bar{Q}_0 \notin \{\bar{Q}(\cdot; \theta, \epsilon) : (\theta, \epsilon) \in \Theta \times \mathcal{E}\}$, it holds that $\Psi(Q_{\theta_0,\epsilon_0}) = \Psi(Q_0)$. This remarkable equality and the convergence of (θ_n, ϵ_n) to (θ_0, ϵ_0) are evidently the keys to the consistency of $\psi_n^* = \Psi(Q_n^*)$. We will also investigate how the consistency result stated in Proposition 29.4 translates into the consistency of the TMLE.

The proof of (1) in Proposition 29.4 is very simple and typical of robust statistical studies. Indeed, $0 = P_{Q_0,G^*(\theta_0)} \frac{\partial}{\partial \epsilon} \ell_{\theta_0,\epsilon}|_{\epsilon=\epsilon_0}$, while the latter expression simplifies as follows:

$$\begin{aligned} &E_{Q_0,G^*(\theta_0)}\left(\frac{2A-1}{G^*(\theta_0)(A \mid V)}(Y - \bar{Q}(A, W; \theta_0, \epsilon_0))\right) \\ &\quad = E_{Q_0,G^*(\theta_0)}\left((\bar{Q}_0(1, W) - \bar{Q}(1, W; \theta_0, \epsilon_0)) - (\bar{Q}_0(0, W) - \bar{Q}(0, W; \theta_0, \epsilon_0))\right) \\ &\quad = \Psi(Q_0) - \Psi(Q_{\theta_0.\epsilon_0}). \end{aligned}$$

This proves (1).

The proof of (2) in Proposition 29.4 fundamentally relies on the fact that (θ_n, ϵ_n) solves the martingale estimating equation $\sum_{i=1}^n D(\theta, \epsilon)(O_i, Z_i) = 0$, where

$$D(\theta, \epsilon)(O, Z) = \frac{1}{g_Z(A \mid V)}\left(\dot{\ell}_{\theta,0}^\top(O) g^r(A \mid V), \frac{\partial}{\partial \epsilon} \ell_{\theta,\epsilon}(O) G^*(\theta)(A \mid V)\right)^\top \tag{29.11}$$

satisfies $P_{Q_0,g_i^*} D(\theta_0, \epsilon_0) = 0$ for all $i \le n$. We have that

$$D(\theta, \epsilon)(O, Z) = \left(D_1(\theta)^\top(O), \frac{\frac{\partial}{\partial \epsilon} \ell_{\theta,\epsilon}(O) G^*(\theta)(A \mid V)}{g_Z(A \mid V)}\right)^\top$$

is an extension of $D_1(\theta)(O)$, which we introduced earlier when summarizing the proof of Proposition 29.2. Here, too, the proof involves the Kolmogorov strong law of large numbers for martingales (Chambaz and van der Laan 2010, Theorem 8), which yields that $n^{-1} \sum_{i=1}^n P_{Q_0,g_i^*} D(\theta_n, \epsilon_n)$ converges to zero almost surely. This results in the convergence in probability of (θ_n, ϵ_n) to (θ_0, ϵ_0) by a Taylor expansion of $(\theta, \epsilon) \mapsto (P_{Q_0,g^r} \dot{\ell}_{\theta,0}^\top, P_{Q_0,G^*(\theta)} \frac{\partial}{\partial \epsilon} \ell_{\theta,\epsilon})$ at (θ_0, ϵ_0). Note that assumption A3 is a clear counterpart of assumption A1 from Proposition 29.2 but that there is no counterpart of assumption A2 from Proposition 29.2 in Proposition 29.4. Indeed, it automatically holds in the framework of the proposition that $-P_{Q_0,G^*(\theta_0)} \frac{\partial^2}{\partial \epsilon^2} \ell_{\theta_0,\epsilon_0} > 0$, while the proof requires that the latter quantity be different from zero.

We now state and comment on a central limit theorem for the stacked estimator (θ_n, ϵ_n) (van der Laan 2008b, Theorem 9). Let us introduce, for all $(\theta, \epsilon) \in \Theta \times \mathcal{E}$,

$$\widetilde{D}(\theta, \epsilon)(O) = (\dot{\ell}_{\theta,0}(O) g^r(A \mid V), \frac{\partial}{\partial \epsilon} \ell_{\theta,\epsilon}(O) G^*(\theta)(A \mid V)),$$

so that $D(\theta, \epsilon)(O, Z)$, defined in (29.11), can be represented as $\widetilde{D}(\theta, \epsilon)(O)/g_Z(A \mid V)$.

Proposition 29.5. *Suppose that assumptions A1, A2 and A3 from Propositions 29.2 and 29.4 hold. In addition, assume that:*

A4. *Under Q_0, the outcome Y is not a deterministic function of (A, W).*

Then the following asymptotic linear expansion holds:

$$\sqrt{n}\left((\theta_n, \epsilon_n) - (\theta_0, \epsilon_0)\right) = S_0^{-1} \frac{1}{\sqrt{n}} \sum_{i=1}^{n} D(\theta_0, \epsilon_0)(O_i, Z_i) + o_P(1), \tag{29.12}$$

where

$$S_0 = E_{Q_0, G^*(\theta_0)} \begin{pmatrix} \ddot{\ell}_{\theta_0,0}(O) \frac{g^r(A|V)}{G^*(\theta_0)(A|V)} & 0 \\ \left[\frac{\partial^2}{\partial\theta\partial\epsilon}\ell_{\theta,\epsilon}(O)G^*(\theta)(A \mid V)\right]\Big|^{\top}_{(\theta,\epsilon)=(\theta_0,\epsilon_0)} \frac{1}{G^*(\theta_0)(A|V)} & \frac{\partial^2}{\partial\epsilon^2}\ell_{\theta_0,\epsilon}(O)|_{\epsilon=\epsilon_0} \end{pmatrix}$$

is an invertible matrix. Furthermore, (29.12) entails that $\sqrt{n}((\theta_n, \epsilon_n) - (\theta_0, \epsilon_0))$ converges in distribution to the centered Gaussian distribution with covariance matrix $S_0^{-1}\Sigma_0(S_0^{-1})^{\top}$, where

$$\Sigma_0 = E_{Q_0, G^*(\theta_0)} \left(\frac{\widetilde{D}(\theta_0, \epsilon_0)\widetilde{D}(\theta_0, \epsilon_0)^{\top}(O)}{G^*(\theta_0)(A \mid V)^2} \right)$$

is a positive definite symmetric matrix. Moreover, S_0 is consistently estimated by

$$S_n = \frac{1}{n} \sum_{i=1}^{n} \begin{pmatrix} \ddot{\ell}_{\theta_n,0}(O_i) \frac{g^r(A_i|V_i)}{g_{Z_i}(A_i|V_i)} & 0 \\ \left[\frac{\partial^2}{\partial\theta\partial\epsilon}\ell_{\theta,\epsilon}(O_i)G^*(\theta)(A_i \mid V_i)\right]\Big|^{\top}_{(\theta,\epsilon)=(\theta_n,\epsilon_n)} \frac{1}{g_{Z_i}(A_i|V_i)} & \frac{\partial^2}{\partial\epsilon^2}\ell_{\theta_n,\epsilon}(O_i)|_{\epsilon=\epsilon_n} g_{Z_i}(A_i \mid V_i) \end{pmatrix},$$

and Σ_0 is consistently estimated by

$$\Sigma_n = \frac{1}{n} \sum_{i=1}^{n} D(\theta_n, \epsilon_n)D(\theta_n, \epsilon_n)^{\top}(O_i, Z_i).$$

We will investigate how the above central limit theorem translates into a central limit theorem for the TMLE. The proof of Proposition 29.5 still relies on the fact that (θ_n, ϵ_n) solves the martingale estimating equation $\sum_{i=1}^{n} D(\theta, \epsilon)(O_i, Z_i) = 0$. It involves the Taylor expansion of $D(\theta, \epsilon)(O, Z)$ at (θ_0, ϵ_0), a multidimensional central limit theorem for martingales and again the Kolmogorov strong law of large numbers (Chambaz and van der Laan 2010, Theorems 8 and 10) . Assumption A4 guarantees that Σ_0 is positive definite.

TMLE is consistent and asymptotically Gaussian. In the first place, the TMLE ψ_n^* is robust: It is a consistent estimator even when the working model is misspecified.

Proposition 29.6. *Suppose that assumptions A1, A2, and A3 from Propositions 29.2 and 29.4 hold. Then the TMLE ψ_n^* consistently estimates the risk difference ψ_0.*

If the design of the RCT was fixed (and, consequently, the n first observations were i.i.d.), then the TMLE would be a robust estimator of ψ_0: Even if the working model is misspecified, then the TMLE still consistently estimates ψ_0 because the treatment mechanism is known (or can be consistently estimated, if one wants to gain in efficiency). Thus, the robustness of the TMLE stated in Proposition 29.6 is the *expected* counterpart of the TMLE's robustness in the latter i.i.d. setting: *Expected* because the TMLE solves a martingale estimating function that is unbiased for ψ_0 at misspecified Q and correctly specified g_i, $i = 1, \ldots, n$.

The proof of Proposition 29.6 is twofold and will now be described. Setting $Q_n^\sim = (Q_W(\cdot; P_0), Q_{Y|A,W}(\cdot; \theta_n, \epsilon_n))$, a continuity argument, and the convergence in probability of the stacked estimator (θ_n, ϵ_n) to (θ_0, ϵ_0) entail the convergence in probability of $\Psi(Q_n^\sim)$ to $\Psi(Q_{\theta_0,\epsilon_0}) = \psi_0$ [see (1) in Proposition 29.4]. The conclusion follows because $\psi_n^* - \Psi(Q_n^\sim)$ converges almost surely to zero by the Glivenko–Cantelli theorem [which, roughly speaking, guarantees that $P_n f$ converges almost surely to $P_0 f$ uniformly in $f \in \mathcal{F} = \{\bar{Q}(1, \cdot; \theta, \epsilon) - \bar{Q}(0, \cdot; \theta, \epsilon) : (\theta, \epsilon) \in \Theta \times \mathcal{E}\}$ because the set $\mathcal{F}$ is moderately complex].

The TMLE ψ_n^* is also asymptotically linear and therefore satisfies a central limit theorem. To see this, let us introduce the real-valued function ϕ on $\Theta \times \mathcal{E}$ such that $\phi(\theta, \epsilon) = \Psi(Q_{\theta,\epsilon})$. Because function ϕ is differentiable on the interior of $\Theta \times \mathcal{E}$, we denote its gradient at (θ, ϵ) with $\phi'_{\theta,\epsilon}$. The latter gradient satisfies

$$\phi'_{\theta,\epsilon} = E_{Q_{\theta,\epsilon},G^*(\theta)} \left\{ D^*(O; P_{Q_{\theta,\epsilon},G^*(\theta)}) \left(\tfrac{\partial}{\partial\theta} \ell_{\theta,\epsilon}^\top(O), \tfrac{\partial}{\partial\epsilon} \ell_{\theta,\epsilon}(O) \right)^\top \right\}.$$

Note that the right-hand-side expression cannot be computed explicitly because the marginal distribution $Q_W(\cdot; P_0)$ is unknown. By the law of large numbers (independent case), we can build an estimator ϕ'_n of $\phi'_{\theta_0,\epsilon_0}$ as follows. For B a large number (say $B = 10^4$), simulate B independent copies $\tilde{O}_b$ of O from the data-generating distribution $P_{Q_n^\sim,G^*(\theta_n)}$, and compute

$$\phi'_n = \frac{1}{B} \sum_{b=1}^{B} D^*(O_b; P_{Q_n^\sim,G^*(\theta_n)}) \left(\tfrac{\partial}{\partial\theta} \ell_{\theta,\epsilon_n}^\top(O_b)|_{\theta=\theta_n}, \tfrac{\partial}{\partial\epsilon} \ell_{\theta_n,\epsilon}(O_b)|_{\epsilon=\epsilon_n} \right)^\top.$$

Proposition 29.7. *Suppose that assumptions A1, A2, A3, and A4 from Propositions 29.2, 29.4, and 29.5 hold. Then the following asymptotic linear expansion holds:*

$$\sqrt{n}(\psi_n^* - \psi_0) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \mathrm{IC}(O_i, Z_i) + o_P(1), \tag{29.13}$$

where

$$\mathrm{IC}(O, Z) = D_1^*(W; Q_{\theta_0,\epsilon_0}) + \phi'^\top_{\theta_0,\epsilon_0} S_0^{-1} D(\theta_0, \epsilon_0)(O, Z). \tag{29.14}$$

Furthermore, (29.13) entails that $\sqrt{n}(\psi_n^* - \psi_0)$ converges in distribution to the centered Gaussian distribution with a variance consistently estimated by

$$s_n^2 = \frac{1}{n}\sum_{i=1}^{n} D_1^*(W_i; Q_n^*)^2 + \frac{2}{n}\sum_{i=1}^{n} D_1^*(W_i; Q_n^*)\phi_n'^{\top} S_n^{-1} D(\theta_n, \epsilon_n)(O_i, Z_i) + (\phi_n'^{\top} S_n^{-1})\Sigma_n(\phi_n'^{\top} S_n^{-1})^{\top}.$$

Proposition 29.7 is the backbone of the statistical analysis of adaptive group sequential RCTs as constructed in Sect. 29.4. In particular, denoting the $(1-\alpha)$-quantile of the standard normal distribution by $\xi_{1-\alpha}$, the proposition guarantees that the asymptotic level of the confidence interval

$$\left[\psi_n^* \pm \frac{s_n}{\sqrt{n}}\xi_{1-\alpha/2}\right], \tag{29.15}$$

for the risk difference ψ_0 is $(1-\alpha)$.

The proof of (29.13) relies again on writing $\sqrt{n}(\psi_n^* - \psi_0) = \sqrt{n}(\psi_n^* - \Psi(Q_n^{\sim})) + \sqrt{n}(\Psi(Q_n^{\sim}) - \psi_0)$. It is easy to derive the asymptotic linear expansion of the first term [the influence function is $D_1^*(\cdot; Q_{\theta_0,\epsilon_0})$]. Moreover, the delta method and (29.12) provides the asymptotic linear expansion of the second term. Thus, the influence function IC is known in closed form. A central limit theorem for martingales (Chambaz and van der Laan 2010, Theorem 9) applied to (29.13) yields the stated convergence and validates the use of s_n^2 as an estimator of the asymptotic variance.

Extensions. We *conjecture* that the influence function IC computed at (O, Z), (29.14), is equal to

$$D_1^*(W; Q_{\theta_0,\epsilon_0}) + D_2^*(O; P_{Q_{\theta_0,\epsilon_0},G^*(\theta_0)})\frac{G^*(\theta_0)(A \mid V)}{g_Z(A \mid V)}.$$

This conjecture is backed by the simulations that we carry out and present in Sect. 29.6. We will tackle the proof of the conjecture in future work. Let us assume for the moment that the conjecture is true. Then the asymptotic linear expansion (29.13) now implies that the asymptotic variance of $\sqrt{n}(\psi_n^* - \psi_0)$ can be consistently estimated by

$$s_n^{*2} = \frac{1}{n}\sum_{i=1}^{n}\left(D_1^*(W_i; Q_n^*) + D_2^*(O_i; P_{Q_n^*,G^*(\theta_n)})\frac{G^*(\theta_n)(A_i \mid V_i)}{g_{Z_i}(A_i \mid V_i)}\right)^2,$$

another independent argument showing that s_n^{*2} converges toward

$$\mathrm{var}_{Q_0,G^*(\theta_0)} D^*(O; P_{Q_{\theta_0,\epsilon_0},G^*(\theta_0)}),$$

i.e., the variance under the fixed design $P_{Q_0,G^*(\theta_0)}$ of the efficient influence curve at $P_{Q_{\theta_0,\epsilon_0},G^*(\theta_0)}$.

Furthermore, the most essential characteristic of the joint methodologies of design adaptation and TMLE is certainly the utmost importance of the role played by

the *likelihood*. The targeted maximized log-likelihood of the data

$$\sum_{i=1}^{n} \left(\log Q_W(W_i; P_n) + \log Q_{Y|A,W}(O_i; \theta_n, \epsilon_n)\right),$$

provides us with a quantitative measure of the quality of the fit of the TLME of Q_0 (targeted toward the parameter of interest). It is therefore possible, for example, to use that quantity for the sake of selection among different working models for Q_0. As with TMLE for i.i.d. data, we can use likelihood-based cross-validation to select among more general initial estimators indexed by fine-tuning parameters. The validity of such TMLEs for the group sequential adaptive designs as studied in this chapter is outside the scope of this chapter.

29.6 Simulations

We characterize the component $Q_0 = Q(\cdot; P_0)$ of the true distribution P_0 of the data structure $O = (W, A, Y)$ as follows. The baseline covariate $W = (U, V)$ where U is uniformly distributed over the unit interval $[0, 1]$, and the subgroup membership covariate $V \in \mathcal{V} = \{1, 2, 3\}$ (hence $v = 3$) satisfies $P_0(V = 1) = 1/2, P_0(V = 2) = 1/3$, and $P_0(V = 3) = 1/6$. The conditional distribution of Y given (A, W) is the gamma distribution characterized by the conditional mean $\bar{Q}_0(Y \mid A, W) = 2U^2 + 2U + 1 + AV + (1 - A)/(1 + V)$ and the conditional standard deviation $\sqrt{\text{var}_{P_0}(Y \mid A, W)} = U + A(1 + V) + (1 - A)/(1 + V)$. The risk difference $\psi_0 = \Psi(Q_0)$, our parameter of interest, is known in closed form $\psi_0 = 91/72 \simeq 1.264$, as is the variance: $v^b(Q_0) = \text{var}_{Q_0,g^b} D^*(O; P_{Q_0,g^b})$ of the efficient influence curve under balanced sampling. The numerical value of $v^b(Q_0)$ is reported in Table 29.1.

We target the design that (a) depends on the baseline covariate $W = (U, V)$ only through V (i.e., belongs to $\mathcal{G}_1$) and (b) minimizes the variance of the efficient influence curve of the parameter of interest Ψ. The latter treatment mechanism $g^*(Q_0)$ and optimal efficient asymptotic variance $v^*(Q_0) = \text{var}_{Q_0,g^*(Q_0)} D^*(O; P_{Q_0,g^*(Q_0)})$ are also known in closed form, and numerical values are reported in Table 29.1.

Table 29.1 Numerical values of the allocation probabilities and variance of the efficient influence curve. The ratio of the variances of the efficient influence curve under targeted optimal and balanced sampling schemes satisfies $R(Q_0) = v^*(Q_0)/v^b(Q_0) \simeq 0.762$

Sampling scheme (Q_0, g)	Allocation probabilities			Variance
	$g(1 \mid v = 1)$	$g(1 \mid v = 2)$	$g(1 \mid v = 3)$	$\text{var}_{Q_0,g} D^*(O; P_{Q_0,g})$
(Q_0, g^b)-balanced	1/2	1/2	1/2	23.864
$(Q_0, g^*(Q_0))$-optimal	0.707	0.799	0.849	18.181

Let $n = (100, 250, 500, 750, 1000, 2500, 5000)$ be a sequence of sample sizes. We estimate $M = 1000$ times the risk difference $\psi_0 = \Psi(Q_0)$ based on $\mathbf{O}^m_{n_7}(n_i)$, $m = 1, \ldots, M$, $i = 1, \ldots, 7$, under i.i.d. (Q_0, g^b)-balanced sampling, i.i.d. $(Q_0, g^*(Q_0))$-optimal sampling, and $(Q_0, \mathbf{g}^*_{n_7})$-adaptive sampling. Finally, we emphasize that the data structure $O = (W, A, Y)$ is not bounded, whereas O is assumed bounded in Propositions 29.2–29.7.

For each $v \in \mathcal{V}$, let us denote $\theta(v) = (\beta_v, \sigma^2_v(0), \sigma^2_v(1))^\top \in \Theta_v$, where $\Theta_v \subset \mathbb{R}^3 \times \mathbb{R}^*_+ \times \mathbb{R}^*_+$ is compact, and $\beta_v = (\beta_{v,1}, \beta_{v,2}, \beta_{v,3})$ [$b = 3$ in (29.5)] is the vector of regression coefficients. Let $\theta = (\theta_1^\top, \theta_2^\top, \theta_3^\top)^\top \in \Theta = \Theta_1 \times \Theta_2 \times \Theta_3$. Following the description in Sect. 29.4.1, the working model $\mathcal{Q}^w_n$ that the TMLE methodology relieson is characterized by the conditional likelihood of Y given (A, W):

$$Q_{Y|A,W}(O; \theta) = \frac{1}{\sqrt{2\pi\sigma^2_V(A)}} \exp\left\{-\frac{(Y - m(A, W; \beta_V))^2}{2\sigma^2_V(A)}\right\},$$

where the conditional mean $\bar{Q}(Y; A, W; \theta)$ of Y given (A, W) is modeled as

$$\bar{Q}(Y; A = a, W = w; \theta) = m(a, w; \beta_v) = \beta_{v,1} + \beta_{v,2}u + \beta_{v,3}a,$$

for all $a \in \mathcal{A}$ and $w = (u, v) \in \mathcal{W} = \mathbb{R} \times \mathcal{V}$. As required, the parameterization condition is met. Obviously, the working model is heavily misspecified: a Gaussian conditional likelihood is used instead of a gamma conditional likelihood, and the parametric forms of the conditional expectation and variance are wrong, too.

Regarding the choice of a reference fixed design $g^r \in \mathcal{G}_1$ (Sect. 29.4.1), we select $g^r = g^b$, the balanced design. The parameter θ_0 only depends on Q_0 and the working model, but its estimator θ_n depends on g^r, which may negatively affect its performance. Therefore, we propose to dilute the impact of the choice of g^r as an initial reference design as follows. For a given sample size n, we first compute a first estimate θ^1_n of θ_0 as in (29.6) but with $\lceil n/4 \rceil$ (the smallest integer not smaller than $n/4$) substituted for n in the sum. Then θ_n is computed as in (29.6), but this time with $G^*(\theta^1_n)(A_i|V_i)$ substituted for $g^r(A_i|V_i)$. The proofs can be adapted to incorporate this modification of the procedure. We refer the interested reader to van der Laan (2008b, Section 8.5).

We update the design each time $c = 25$ new observations are sampled. In addition, the first update only occurs when there are at least 5 completed observations in each treatment arm and for all V-strata. Thus, the minimal sample size at the first update is 30, and it can be shown that, under the balanced design, the expected sample size at the first sample size at which there are at least 5 observations in each arm equals 75. Finally, as a precautionary measure, we systematically apply a thresholding to the updated treatment mechanism: Using the notation of Sect. 29.4, we substitute $\max\{\delta, \min\{1 - \delta, g^*_i(A_i \mid V_i)\}\}$ to $g^*_i(A_i \mid V_i)$ in all computations. We arbitrarily choose $\delta = 0.01$.

We now invoke the central limit theorem stated in Proposition 29.7 to construct confidence intervals for the risk difference. Let us introduce, for all types of sampling and each sample size n_i, the confidence intervals

$$\mathcal{I}_{n_i,m} = \left[\psi^*_{n_i}(\mathbf{O}^m_{n_7}(n_i)) \pm \sqrt{\frac{v_{n_i}(\mathbf{O}^m_{n_7}(n_i))}{n_i}} \xi_{1-\alpha/2} \right], \quad m = 1, \ldots, M,$$

where the definition of the variance estimator $v_n(\mathbf{O}^m_{n_7}(n))$ based on the n first observations $\mathbf{O}^m_{n_7}(n)$ depends on the sampling scheme. Under i.i.d. (Q_0, g^b)-balanced sampling, $v_n(\mathbf{O}^m_{n_7}(n))$ is the estimator of the asymptotic variance of the TMLE $\Psi(Q^*_{n,\mathrm{iid}})$:

$$v_n(\mathbf{O}^m_{n_7}(n)) = \frac{1}{n} \sum_{i=1}^{n} D^*(O^m_i; P_{Q^*_{n,\mathrm{iid}}, g^b})^2. \tag{29.16}$$

Under i.i.d. $(Q_0, g^*(Q_0))$-optimal sampling, $v_n(\mathbf{O}^m_{n_7}(n))$ is defined as in (29.16), replacing g^b with $g^*(Q_0)$. Lastly, under $(Q_0, \mathbf{g}^*_n)$-adaptive sampling, $v_n(\mathbf{O}^m_{n_7}(n)) = s^{*2}_n(\mathbf{O}^m_{n_7}(n))$, the estimator of the conjectured asymptotic variance of $\sqrt{n}(\psi^*_n(\mathbf{O}^m_{n_7}(n)) - \psi_0)$ computed on the n first observations $\mathbf{O}^m_{n_7}(n)$. We are interested in the empirical coverage (reported in Table 29.2, top rows) $c_{n_i} = 1/M \sum_{m=1}^{M} I(\psi_0 \in \mathcal{I}_{n_i,m})$ guaranteed for each sampling scheme and every $i = 1, \ldots, 7$ by $\{\mathcal{I}_{n_i,m} : m = 1, \ldots, M\}$. The rescaled empirical coverage proportions Mc_{n_i} should have a binomial distribution with parameter $(M, 1-a)$ and $a = \alpha$ for every $i = 1, \ldots, 7$. This property can be tested in terms of a standard binomial test, the alternative hypothesis stating that $a > \alpha$. This results in a collection of seven p-values for each sampling scheme, as reported in Table 29.2 (bottom rows).

Considering each sampling scheme (i.e., each row of Table 29.2) separately, we conclude that the $(1-\alpha)$-coverage cannot be declared defective under i.i.d. (Q_0, g^b)-balanced sampling for any sample size $n_i \geq n_3 = 500$, i.i.d. $(Q_0, g^*(Q_0))$-optimal sampling for any sample size $n_i \geq n_2 = 250$, and $(Q_0, \mathbf{g}^*_{n_7})$-adaptive sampling for any sample size $n_i \geq n_1 = 100$, adjusting for multiple testing in terms of the Benjamini–Yekutieli procedure for controlling the false discovery rate at level 5%.

This is a remarkable result that not only validates the theory but also provides us with insight into the finite sample properties of the TMLE procedure based on adaptive sampling. The fact that the TMLE procedure behaves better under an adaptive sampling scheme than under balanced i.i.d. sampling scheme at sample size $n_1 = 100$ may not be due to mere chance only. Although the TMLE procedure based

Table 29.2 Checking the validity of the coverage of our simulated confidence intervals, values c_{n_i} (top row), p-values (bottom row, between parentheses)

Sampling scheme	Sample size						
	n_1	n_2	n_3	n_4	n_5	n_6	n_7
i.i.d. (Q_0, g^b)-balanced	0.913	0.925	0.939	0.934	0.945	0.940	0.946
	($p < 0.001$)	($p < 0.001$)	(0.067)	(0.015)	(0.253)	(0.087)	(0.300)
i.i.d. $(Q_0, g^*(Q_0))$-optimal	0.894	0.941	0.940	0.953	0.954	0.947	0.947
	($p < 0.001$)	(0.111)	(0.087)	(0.688)	(0.739)	(0.351)	(0.351)
adaptive $(Q_0, \mathbf{g}^*_{n_7})$	0.934	0.939	0.956	0.945	0.943	0.933	0.952
	(0.015)	(0.067)	(0.827)	(0.253)	(0.172)	(0.011)	(0.634)

on an adaptive sampling scheme is initiated under the balanced sampling scheme (so that each stratum consists at the beginning of comparable numbers of patients assigned to each treatment arm, allowing one to estimate, at least roughly, the required parameters), it starts deviating from it [as soon as every (A, V)-stratum counts 5 patients)] each time 25 new observations are accrued. The poor performance of the TMLE procedure based on an optimal i.i.d. sampling scheme at sample size n_1 is certainly due to the fact that, by starting directly from the optimal sampling scheme (a choice we would not recommend in practice), too few patients from stratum $V = 3$ are assigned to treatment arm $A = 0$ among the n_1 first subjects. At larger sample sizes, the TMLE procedure performs equally well under an adaptive sampling scheme and under both i.i.d. schemes in terms of coverage.

Now that we know that the TMLE-based confidence intervals based on $(Q_0, \mathbf{g}_n^*)$-adaptive sampling are valid confidence regions, it is of interest to compare the widths of the latter adaptive-sampling $(Q_0, \mathbf{g}_n^*)$-confidence intervals with their counterparts obtained under i.i.d. (Q_0, g^b)-balanced or $(Q_0, g^*(Q_0))$ optimal sampling schemes. For this purpose, we compare, for each sample size n_i, the empirical distribution of $\{\sqrt{v_n(\mathbf{O}_{n_7}^m(n_i))} : m = 1, \ldots, M\}$ as in (29.16) [i.e., the empirical distribution of width of the TMLE-based confidence intervals at sample size n_i obtained under i.i.d (Q_0, g^b)-balanced sampling, up to the factor $2\xi_{1-\alpha/2}/\sqrt{n_i}$] to the empirical distribution of $\{s_n^*(\mathbf{O}_{n_7}^m(n_i)) : m = 1, \ldots, M\}$ [i.e., the empirical distribution of the width of the TMLE-based confidence intervals at sample size n_i obtained under $(Q_0, \mathbf{g}_n^*)$-adaptive sampling, up to the factor $2\xi_{1-\alpha/2}/\sqrt{n_i}$] in terms of the two-sample Kolmogorov–Smirnov test, where the alternative states that the confidence intervals obtained under adaptive sampling are stochastically smaller than their counterparts under i.i.d. balanced sampling. This results in seven p-values, all equal to zero, which we nonetheless report in Table 29.3 (bottom row). In order to get a sense of how much narrower the confidence intervals obtained under adaptive sampling are, we also compute and report in Table 29.3 (top row) the ratios of empirical average widths:

$$\frac{\frac{1}{M}\sum_{m=1}^{M} s_n^*(\mathbf{O}_{n_7}^m(n_i))}{\frac{1}{M}\sum_{m=1}^{M} \sqrt{v_n(\mathbf{O}_{n_7}^m(n_i))}}, \tag{29.17}$$

for each sample size n_i. Informally, this shows a 12% gain in width.

On the other hand, we also compare, for each sample size n_i, the empirical distribution of $\{\sqrt{v_n(\mathbf{O}_{n_7}^m(n_i))} : m = 1, \ldots, M\}$, as in (29.16), but replacing g^b by $g^*(Q_0)$ [i.e., the empirical distribution of width of the TMLE-based confidence intervals at sample size n_i obtained under i.i.d. $(Q_0, g^*(Q_0))$-optimal sampling, up to the factor $2\xi_{1-\alpha/2}/\sqrt{n_i}$] to the empirical distribution of $\{s_n^*(\mathbf{O}_{n_7}^m(n_i)) : m = 1, \ldots, M\}$ [i.e., the empirical distribution of the width of the TMLE-based confidence intervals at sample size n_i obtained under $(Q_0, \mathbf{g}_n^*)$-adaptive sampling, up to the factor $2\xi_{1-\alpha/2}/\sqrt{n_i}$] in terms of the two-sample Kolmogorov–Smirnov test, the alternative stating that the confidence intervals obtained under adaptive sampling are stochastically larger than their counterparts under i.i.d. optimal sampling. This results in seven p-values that we report in Table 29.3 (bottom row). In order to get a sense of how similar the confidence intervals obtained under adaptive and i.i.d. optimal sampling schemes

Table 29.3 Comparing the width of our confidence intervals with the ratios of average widths as defined in (29.17) and p-values (bottom rows, between parentheses)

Comparison	Sample size						
	n_1	n_2	n_3	n_4	n_5	n_6	n_7
$(Q_0, \mathbf{g}^*_{n_7})$ vs. (Q_0, g^b)	0.856	0.871	0.879	0.880	0.878	0.877	0.876
	(0)	(0)	(0)	(0)	(0)	(0)	(0)
$(Q_0, \mathbf{g}^*_{n_7})$ vs. $(Q_0, g^*(Q_0))$	0.962	0.977	0.992	0.995	0.997	1.000	1.000
	(0.144)	(0.236)	(0.100)	(0.060)	(0.407)	(0.236)	(0.144)

are, we also compute and report for each sample size n_i in Table 29.3 (top row) the ratios of empirical average widths as in (29.17) replacing again g^b by $g^*(Q_0)$ in the definition (29.16) of $v_n(\mathbf{O}^m_{n_7}(n))$. Informally, this shows that the confidence intervals obtained under adaptive sampling are even slightly narrower in average than their counterparts obtained under i.i.d. optimal sampling.

Illustration. So far we have been concerned with distributional results, and we now investigate a particular arbitrarily selected simulated trajectory of the TMLE, the confidence intervals, and the adaptive design g^*_n as a function of sample size. Some interesting features of the selected simulated trajectory are apparent in Fig. 29.2 and Table 29.4. For instance, we can follow the convergence of the TMLE ψ^*_n toward the true risk difference ψ_0 in the top plot of Fig. 29.2 and in the fifth column of Table 29.4. Similarly, the middle plot of Fig. 29.2 and the second to fourth columns of Table 29.4 illustrate the convergence of $\mathbf{g}^*_n$ toward $G^*(\theta_0)$, as stated in Proposition 29.3. What these plots and columns also teach us is that, in spite of the misspecified working model, the learned design $G^*(\theta_0)$ seems very close to the optimal treatment mechanism $g^*(Q_0)$ for the chosen simulation scheme and working model used in our simulation study. Moreover, the last column of Table 29.4 illustrates how the confidence intervals $[\psi^*_n \pm s^*_n \xi_{1-0.05/2}/\sqrt{n}]$ shrink around the true risk difference ψ_0 as the sample size increases.

Yet, the bottom plot of Fig. 29.2 may be the most interesting of the three. It obviously illustrates the convergence of s^{*2}_n toward $\mathrm{var}_{Q_0,G^*(\theta_0)} D^*(O; P_{Q_{\theta_0,\epsilon_0},G^*(\theta_0)})$, i.e., toward the variance under the fixed-design $P_{Q_0,G^*(\theta_0)}$ of the efficient influence curve at $P_{Q_{\theta_0,\epsilon_0},G^*(\theta_0)}$. Hence, it also teaches us that the latter limit seems very close to the optimal asymptotic variance $v^*(Q_0)$ for the chosen simulation scheme and working model used in our simulation study. *More importantly,* s^{*2}_n *strikingly converges to* $v^*(Q_0)$ *from below.* This finite sample characteristic may reflect the fact that the true finite sample variance of $\sqrt{n}(\psi^*_n - \psi_0)$ might be lower than $v^*(Q_0)$. Studying this issue in depth is certainly very delicate and goes beyond the scope of this chapter.

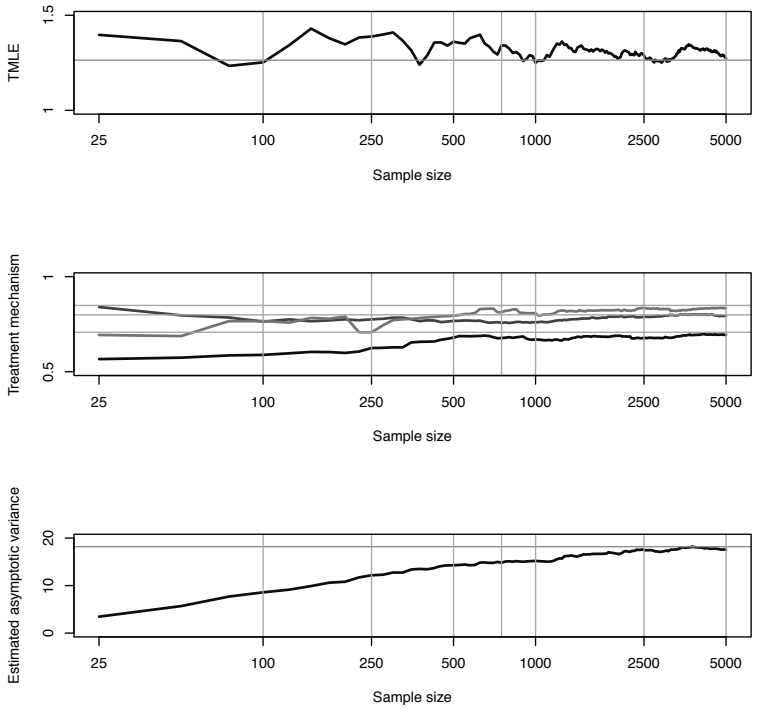

Fig. 29.2 Illustrating the TMLE procedure under $(Q_0, \mathbf{g}_n^*)$-adaptive sampling scheme. *Top plot*: The sequence $\psi_n^*(\mathbf{O}_{n_7}^1(n))$, *horizontal gray line* indicates true value of risk difference ψ_0. *Middle plot*: Three sequences $g_n^*(1 \mid 1) = G^*(\theta_n(\mathbf{O}_{n_7}^1(n)))(1 \mid 1)$ (*bottom curve*), $g_n^*(1 \mid 2) = G^*(\theta_n(\mathbf{O}_{n_7}^1(n)))(1 \mid 2)$ (*middle curve*), and $g_n^*(1 \mid 3) = G^*(\theta_n(\mathbf{O}_{n_7}^1(n)))(1 \mid 3)$ (*top curve*). The three *horizontal gray lines* indicate the optimal allocation probabilities $g^*(Q_0)(1 \mid 1)$ (*bottom line*), $g^*(Q_0)(1 \mid 2)$ (*middle line*), and $g^*(Q_0)(1 \mid 3)$ (*top line*). *Bottom plot*: The sequence s_n^{*2} of estimated asymptotic variance of $\sqrt{n}(\psi_n^* - \psi_0)$, *horizontal gray line* indicates the value of the optimal variance $v^*(Q_0)$. (The x-axis is on a logarithmic scale for all plots)

Table 29.4 Simulation results of the TMLE procedure under a $(Q_0, \mathbf{g}_n^*)$-adaptive sampling scheme

Sample size	Allocation probabilities			TMLE	confidence interval
n	$g_n^*(1 \mid 1)$	$g_n^*(1 \mid 2)$	$g_n^*(1 \mid 3)$	ψ_n^*	$(\psi_n^* \pm s_n^* \xi_{1-0.05/2} / \sqrt{n})$
n_1	0.589	0.764	0.766	1.252	(0.722,1.783)
n_2	0.624	0.775	0.707	1.388	(0.974,1.802)
n_3	0.679	0.767	0.795	1.361	(1.037,1.685)
n_4	0.677	0.757	0.813	1.341	(1.068,1.615)
n_5	0.670	0.760	0.806	1.250	(1.012,1.488)
n_6	0.677	0.788	0.835	1.288	(1.126,1.451)
n_7	0.694	0.793	0.834	1.273	(1.157,1.389)

Concluding Remarks

We developed the TMLE in group sequential adaptive designs for the data structure $O = (W, A, Y)$. This generalizes the TMLE for the i.i.d. design for this data structure O as covered in depth by the first part of this book. In addition, we showed that targeted learning goes beyond targeted estimation and starts with the choice of design. Our targeted adaptive designs combined with the TMLE provides a fully targeted methodology, including design, for statistical inference with respect to a causal effect of interest. In the previous two chapters, we demonstrated (1) how to fully integrate the state of the art in machine learning while fully preserving the CLT for statistical inference and (2) the application of TMLE for the purpose of obtaining a targeted posterior distribution of the target parameter of interest, thereby improving on the current standard in Bayesian learning.

This book demonstrated that targeted learning with TMLE represents a unified optimal approach for learning from data that can be represented as realizations of n i.i.d. random variables. However, these last three chapters provide insight into the enormous reach of targeted learning, covering Bayesian learning, integrating the most adaptive machine learning algorithms, targeted designs, and statistical inference for targeted adaptive designs that generate dependent data. Further exciting research in these areas is needed, but it appears that targeted learning based on super learning and TMLE provides a road map for developing optimal tools to attack upcoming statistical challenges.