Safe anytime-valid inference: from theory to implementation in psychiatry research
Turner, R.J.

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Curriculum Vitae

From 2010 until 2013 Rosanne studied Medicine at the Leiden University Medical Center (LUMC). She was admitted to the Honours College of Leiden University, where she was awarded a grant to start a research project at the pathology department of LUMC under supervision of Dr. Hans Baelde, Prof. Kitty Bloemenkamp and Prof. J.A. Bruijn. In 2014 she got the opportunity to continue this research full time directly after obtaining her Bachelor degree, which resulted in the PhD thesis *Endothelial Pathology in Preeclampsia* at the Faculty of Medicine of Leiden University.

During her time as a researcher at LUMC, Rosanne discovered that scientific research and particularly methodology and mathematics interested her the most. Therefore she decided to continue her Master studies in this direction: from 2017 until 2019 she studied Statistical Science for the Life and Behavioral Sciences at the faculty of Science at Leiden University, for which she graduated *cum laude*. During her studies she also worked part-time as a software engineer at El Nino development. She wrote her Master thesis *Safe tests for 2 x 2 contingency tables and the Cochran-Mantel-Haenszel test* under supervision of Prof. Peter Grünwald at CWI, which was awarded the Jan Hemelrijk Award by the Dutch society for statistics and operations research (VVSOR).

After graduating she continued the research on safe statistics started during her master thesis as part of a second PhD trajectory, this time in Mathematics. She worked in the *Enabling Personalized Interventions* consortium under supervision of Prof. Peter Grünwald, Prof. Floortje Scheepers (UMC Utrecht) and Dr. Aki Härmä (Philips research) on implementations of safe statistics and other methods suitable for real-time, federated learning. Rosanne spent half her time focusing on developing statistical methodology in the machine learning group at CWI, and the other half implementing new methods and working as a data scientist at the data science team PsyData at the Psychiatry department of UMC Utrecht. Since finishing her second PhD project, Rosanne has continued working at the Psychiatry department of UMC Utrecht as a clinical data scientist.

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Appendix with Supplementary Material

Supplementary material for chapter 2

Appendix S2.A contains detailed proofs. Appendix S2.B contains a detailed description of the numerical approach to calculating e-variables for restricted $\mathcal{H}_1$. Appendix S2.C contains a detailed description of Gunel-Dickey Bayes factors. Appendix S2.D contains optional stopping experiments. Appendix S2.E explains how to adapt the block group sizes n_a and n_b based on past data.

S2.A Proofs

The proofs below repeatedly use Theorem 1 of Grünwald et al. [2022a] and a direct corollary (called Corollary 2 by Grünwald et al. [2022a]), which we restate here for convenience, combined as a single statement. We use the notation adopted later in the paper: for $\mathcal{H}_0 = \{P_\theta : \theta \in \Theta_0\}$ and, for W a distribution on Θ_0, we write $P_W = \int P_\theta dW(\theta)$.

Theorem (Theorem 1 of Grünwald et al. [2022a]) Let Y be a random variable taking values in a set $\mathcal{Y}$. Suppose Q is a probability distribution for Y with density q that is strictly positive on all of $\mathcal{Y}$ and let $\mathcal{H}_0 = \{P_\theta : \theta \in \Theta_0\}$ be a set of distributions for Y where each P_θ has density p_θ. Let $\mathcal{W}_0$ be the set all distributions on Θ_0. Assume $\inf_{W_0 \in \mathcal{W}_0(\Theta_0)} D(Q \| P_{W_0}) < \infty$. Then (a) there exists a (potentially sub-) distribution P_0^* with density p_0^* such that

$$S^* := \frac{q(Y)}{p_0^*(Y)}$$

is an e-variable (p_0^* is called the *Reverse Information Projection (RIPr) of* q *onto* $\{p_W : W \in \mathcal{W}_0\}$ [Li, 1999, Li and Barron, 2000, Grünwald et al., 2022a]). Moreover, (b), S^* satisfies

$$\sup_{S \in \mathcal{E}(\Theta_0)} \mathbf{E}_{Y \sim Q}[\log S] = \mathbf{E}_{Y \sim Q}[\log S^*] = \inf_{W_0 \in \mathcal{W}_0(\Theta_0)} D(Q \| P_{W_0}) = D(Q \| P_0^*). \tag{A.1}$$

and is thus the Q-GRO e-variable for Y. If the minimum is achieved by some W_0^*, i.e. $D(Q\|P_0^*) = D(Q\|P_{W_0^*})$, then $P_0^* = P_{W_0^*}$. Moreover, (c), if there exists an e-variable S of the form $q(Y)/p_{W_0}(Y)$ for some $W_0 \in \mathcal{W}_0$ then W_0 must achieve the infimum in (A.1) and S must be essentially equal to S^* in the sense that for all $P \in \mathcal{H}_0 \cup \{Q\}$, $P(S^* = q(Y)/p_{W_0}(Y)) = 1$. Similarly (d), if there exists a $W_0^* \in \mathcal{W}_0$ that achieves the infimum in (A.1) then $S = q(Y)/p_{W_0^*}(Y)$ is an e-variable and S is again essentially equal to S^*.

S2.A.1 Proof of Propositions

Proof of Proposition 1 Below we state and prove a slight generalization of Proposition 1.

Proposition 4 (generalization)**.** Let $\mathcal{H}_1 = \{Q\}$ be a singleton and let $\mathcal{H}_0 = \{P_\theta : \theta \in \Theta_0\}$ be such that for some distribution W on Θ_0, $D(Q\|P_W) < \infty$. For general $\theta \in \Theta_0$ and distributions W on Θ_0, define $S_{\theta,(j)} := q(Y_{(j)})/p_\theta(Y_{(j)})$ and $S_{W,(j)} = q(Y_{(j)})/p_W(Y_{(j)})$. We have:

1. Suppose there exists a distribution W on Θ_0 such that $S_{W,(1)}$ is an e-variable. Then $S_{W,(1)}$ is the Q-GRO e-variable for $Y_{(1)}$. In particular, if W puts mass 1 on a particular $\theta^\circ \in \Theta_0$, then $S_{W,(1)} = S_{\theta^\circ,(1)}$ is the Q-GRO e-variable.

2. If $\Theta_0 = \{\theta_0\}$ is simple then, with the prior W_0 putting mass 1 on θ_0, $S_{W_0,(1)} = S_{\theta_0,(1)}$ is an e-variable and hence, by the above, also the Q-GRO e-variable.

3. If, for some $\theta^\circ \in \Theta_0$, $S_{\theta^\circ,(1)}$ is an e-variable and we further assume that $Y_{(1)}, Y_{(2)}, \ldots$ are i.i.d. according to all distributions in $\mathcal{H}_0 \cup \mathcal{H}_1$, then $S^{(m)}_{\text{GRO}(Q)} = \prod_{j=1}^m S_{\theta^\circ,(j)}$; that is, the Q-GRO optimal (unconditional) e-variable for $Y^{(m)}$ is the product of the individual Q-GRO optimal e-variables.

Proof. Part 1 The theorem above, part (b), implies, with $Y = Y_{(1)}$, that some Q-GRO e-variable S^* for $Y_{(1)}$ exists. Part (c) then implies that we can take S^* to be equal to $S_{W,(1)}$. This implies the statement.

Part 2 is immediate.

Part 3 We assume that $S_{\theta^\circ,(1)}$ is an e–variable. Then the i.i.d. assumption implies that $S^{(m)}_{\theta^\circ} := \prod_{j=1}^m S_{\theta^\circ,(j)} = \prod q(Y_{(j)})/p_{\theta^\circ}(Y_{(j)})$ is also an e-variable. But [Grünwald et al., 2022a, Theorem 1], part (c) as stated above implies (by taking a distribution W putting mass 1 on θ) that for $\mathcal{H}_0$ for which data are i.i.d., for each $m \geq 1$, that if a $\theta \in \Theta_0$ exists such that $S^{(m)}_\theta$ is an e-variable, then $S^{(m)}_\theta$ must be the Q-GRO e-variable for $Y^{(m)}$. This proves the statement. □

Proof of Proposition 2 The formulae for $\breve{\theta}_a|Y^{(j-1)}$ and $\breve{\theta}_b|Y^{(j-1)}$ are standard expressions for the Bayes predictive distribution based on the given beta priors; we omit further details. As to the expression for $\breve{\theta}_0|Y^{(j-1)}$ in terms of $\kappa = n_b/n_a$: Straightforward rewriting gives, for general $\alpha_a, \alpha_b, \beta_a, \beta_b$:

$$\breve{\theta}_0|Y^{(j-1)} = \frac{1}{1+\kappa}\breve{\theta}_a|Y^{(j-1)} + \frac{\kappa}{1+\kappa}\breve{\theta}_b|Y^{(j-1)}. \tag{A.2}$$

If we plug in the expressions for $\breve{\theta}_a|Y^{(j-1)}, \breve{\theta}_b|Y^{(j-1)}$ and we instantiate to $\alpha_b = \kappa\alpha_a$, and $\beta_b = \kappa\beta_a$, this becomes

$$\begin{aligned}\breve{\theta}_0|Y^{(j-1)} &= \frac{1}{1+\kappa}\frac{U_a+\alpha_a}{n_a(j-1)+\alpha_a+\beta_a} + \frac{\kappa}{1+\kappa}\frac{U_b+\alpha_b}{\kappa(n_a(j-1)+\alpha_a+\beta_a)} \\ &= \frac{1}{1+\kappa}\frac{U_a+U_b+(1+\kappa)\alpha_a}{n_a(j-1)+\alpha_a+\beta_a} = \frac{U+(1+\kappa)\alpha_a}{n(j-1)+(1+\kappa)\alpha_a+(1+\kappa)\beta_a},\end{aligned}$$

which is what we had to prove.

S2.A.2 Proof of Theorem 1

We first restate Theorem 1 in its extended version that holds for $k \geq 2$ data streams. Let $\vec{n} = (n_1, \ldots, n_k), n = \sum_{g=1}^{k} n_g, \vec{\theta} = (\theta_a, \ldots, \theta_k) \in \Theta^k$ and $\vec{y}^n$ be as defined in the main text (3.3). We use '$\vec{Y}^n \sim P_{\theta^*}$' as an abbreviation for '$Y_1^{n_1} \sim P_{\theta_1^*}; \ldots; Y_k^{n_k} \sim P_{\theta_k^*}$'.

Theorem .1 (extended)**.** Let

$$s(\vec{y}^n; \vec{n}, \vec{\theta}^*) := \prod_{g=1}^{k} \frac{p_{\theta_g^*}(y_g^{n_g})}{\prod_{i=1}^{n_g}\left(\sum_{g'=1}^{k}\frac{n_{g'}}{n}p_{\theta_{g'}^*}(y_{i,g})\right)}.$$

The random variable $S_{[\vec{n},\vec{\theta}^*]} := s(\vec{Y}^n; \vec{n}, \vec{\theta}^*)$ is an e-variable, i.e. we have:

$$\sup_{\theta\in\Theta} \mathbf{E}_{V^n\sim P_\theta}\left[s(V^n; \vec{n}, \vec{\theta}^*)\right] \leq 1.$$

Moreover, if $\{P_\theta : \theta \in \Theta\}$ is a convex set of distributions, then $S_{[\vec{n},\vec{\theta}^*]}$ is the $(\vec{\theta}^*)$-GRO e-variable: for any non-negative function s' on $\mathcal{Y}^n$ satisfying $\sup_{\theta\in\Theta} \mathbf{E}_{V^n\sim P_\theta}[s'(V^n)] \leq 1$, we have:

$$\mathbf{E}_{\vec{Y}^n\sim P_{\theta^*}}[\log s(\vec{Y}^n; \vec{n}, \vec{\theta}^*)] \geq \mathbf{E}_{\vec{Y}^n\sim P_{\theta^*}}[\log s'(\vec{Y}^n)].$$

Proof of Theorem .1 The following fact plays a central role in the proof:

Fact For $g \in (1, ..., k)$, let $n_g \in \mathbf{N}, n := \sum_{g=1}^{k} n_g$ and let $u_g \in \mathbf{R}^+$. Suppose that $\sum_{g=1}^{k} n_g u_g \leq n$. Then $\prod_{g=1}^{k} u_g^{n_g} \leq 1$.

This result follows from the following standard generalization of Young's inequality to k numbers: for any k numbers $u_1, \ldots, u_k \in \mathbf{R}_0^+$ and any k nonnegative numbers $p_1, \ldots, p_k$ with $\sum_{g=1}^{k} p_g = 1$, we have $\prod_{g=1}^{k} u_g^{p_g} \leq \sum_{g=1}^{k} p_g u_g$. Applying this with $p_g = n_g/n$ to u_g and n_g as above, we get $\prod_{g=1}^{k} u_g^{n_g/n} \leq \sum_{g=1}^{k}(n_g u_g)/n \leq 1$, and the result follows by exponentiating to the power n.

Part 1 For $y \in \mathcal{Y}$, set set $p^\circ(y) := \sum_{g=1}^{k}(n_g/n)p_{\theta_g^*}(y)$ and $p^\circ(y^m) = \prod_{i=1}^{m} p^\circ(y_i)$.

For all $\theta \in \Theta$ we have:

$$\mathbf{E}_{V^n \sim P_\theta}\left[s(V^n; \vec{n}, \vec{\theta}^*)\right] = \prod_{g=1}^{k} \mathbf{E}_{Y_g^{n_g} \sim P_\theta}\left[\frac{p_{\theta_g^*}(Y_g^{n_g})}{p^\circ(Y_g^{n_g})}\right] = \prod_{g=1}^{k}\left(\mathbf{E}_{Y \sim P_\theta}\left[\frac{p_{\theta_g^*}(Y)}{p^\circ(Y)}\right]\right)^{n_g}. \tag{A.3}$$

We also have

$$\sum_{g=1}^{k} \frac{n_g}{n} \mathbf{E}_{Y \sim P_\theta}\left[\frac{p_{\theta_g^*}(Y)}{p^\circ(Y)}\right] = \mathbf{E}_{Y \sim P_\theta}\left[\sum_{g=1}^{k} \frac{n_g}{n} \cdot \frac{p_{\theta_g^*}(Y)}{\sum_{g'=1}^{k} \frac{n_{g'}}{n} p_{\theta_{g'}^*}(Y)}\right] = 1. \tag{A.4}$$

The result now follows by combining (A.3) with (A.4) using the Fact further above.

Part 2 By convexity of $\{P_\theta : \theta \in \Theta\}$, there exists $\theta^\circ \in \Theta$ such that $p_{\theta^\circ} = \sum_{g=1}^{k}(n_g/n)p_{\theta_g^*}$ and then the numerator in (A.4) can we rewritten as $p_{\theta^\circ}(\vec{y})$. The GRO-property is now an immediate consequence of Proposition 4, Part 1.

S2.B Numerical approach to calculating e-variables for restricted $\mathcal{H}_1$

In this subsection we describe how we propose to approximate the beta prior and posterior on the restricted $\mathcal{H}_1$ with parameter space $\Theta(\delta)$, as defined in (5.1). Note that we limit ourselves to $\delta > 0$ in this detailed description; for $\delta < 0$ one can apply an entirely equivalent approach, with an extra term in the reparameterization. We define

$$\zeta = \begin{cases} \delta \text{ if } d((\theta_a, \theta_b)) = \theta_b - \theta_a, \\ 0 \text{ if } d((\theta_a, \theta_b)) = \text{log-odds-ratio}(\theta_a, \theta_b), \end{cases}$$

such that we have $\theta_a \in (0, 1-\zeta)$ and in both cases, θ_b is completely determined by θ_a: $\theta_b = d^{-1}(\delta; \theta_a)$. Hence, our density estimation problem now becomes one-dimensional, which enables us to put a discretized prior on the restricted parameter space.

First, we discretize the parameter space Θ_a to a grid (a vector) with precision $K, K \in (0, 1-\zeta)$ and $1/K \in \mathbb{N}^+$: $\bar{\boldsymbol{\theta}}_{\boldsymbol{a}} = (K, 2K, 3K, \ldots, 1-\zeta)$. Then, we reparameterize $\theta_a = (1-\zeta)\rho$, with $\rho \in (0,1)$. Then, we have $\bar{\boldsymbol{\rho}} = (K/(1-\zeta), 2K/(1-\zeta), \ldots, 1)$. For the discretized grid $\bar{\boldsymbol{\rho}}$, we compute the prior $W = \text{Beta}(\alpha, \beta)$ densities and normalize them, which also gives us the discretized densities for each $\theta_a^i \in \bar{\boldsymbol{\theta}}_{\boldsymbol{a}}$ (with $i \in (1, 2, \ldots, 1/K)$):

$$\pi_{\alpha,\beta,\zeta}(\theta_a^i) = \frac{\text{Beta}(\frac{\theta_a^i}{1-\zeta}; \alpha, \beta)}{\sum_{k=1}^{\frac{1}{K}} \text{Beta}(\frac{\theta_a^k}{1-\zeta}; \alpha, \beta)}.$$

For all elements of $\bar{\boldsymbol{\theta}}_{\boldsymbol{a}}$, the corresponding θ_b is retrieved and the likelihood of incoming data points $p_{\theta_a, \theta_b}(Y^{(j-1)})$ is calculated. We can then estimate the posterior density of $\theta_a^i \in \bar{\boldsymbol{\theta}}_{\boldsymbol{a}}$:

$$p(\theta_a^i | Y^{(j-1)}) = \frac{\pi_{\alpha,\beta,\zeta}(\theta_a^i) p_{\theta_a^i, \theta_b^i}(Y^{(j-1)})}{\sum_{k=1}^{\frac{1}{K}} \pi_{\alpha,\beta,\zeta}(\theta_a^k) p_{\theta_a^k, \theta_b^k}(Y^{(j-1)})}.$$

We can then estimate $\breve{\theta}_a | Y^{(j-1)} = \mathbf{E}_{\theta_a \sim W | Y^{(j-1)}}[\theta_a]$ as $\sum_{i=1}^{\frac{1}{K}} p(\theta_a^i | Y^{(j-1)}) \theta_a^i$, and $\breve{\theta}_b | Y^{(j-1)} = d^{-1}(\delta; \theta_a | Y^{(j-1)})$.

S2.C The Gunel-Dickey Bayes Factors do not give rise to e–variables

Sampling	Fixed	Bayes factor (10) for 2x2 table
Poisson	none	$\frac{8(n+1)(n_1+1)}{(n+4)(n+2)} \left[\frac{n_{a1}! n_{b1}! n_{a0}! n_{b0}! n!}{(n_1+1)! n_0! n_a! n_b!} \right]$
Joint multinomial	n	$\frac{6(n+1)(n_1+1)}{(n+3)(n+2)} \left[\frac{n_{a1}! n_{b1}! n_{a0}! n_{b0}! n!}{(n_1+1)! n_0! n_a! n_b!} \right]$
Independent multinomial	n_a, n_b	$\binom{n}{n_1} / (\binom{n_a}{n_{a1}} \binom{n_b}{n_{b1}}) \frac{(n+1)}{(n_a+1)(n_b+1)}$
Hypergeometric	n_a, n_b, n_1	$\frac{n_{a1}! n_{b1}! n_{a0}! n_{b0}! n!}{\prod_{i \in \{a,b,0,1\}} (n_i + \mathbb{I} n_i = min(n_a, n_b, n_0, n_1))!}$

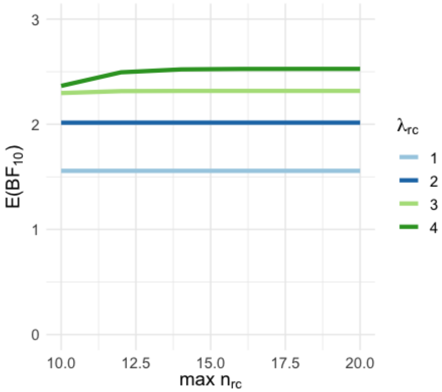
Table S2.1: Overview of (objective) Bayes factors for contingency table testing provided by Gunel and Dickey [1974] and Jamil et al. [2017].

We will not consider the hypergeometric and joint multinomial scenarios for this paper, where the number of successes n_1 is fixed, as they do not match the block-wise data design in this paper. The Bayes factor for the Poisson sampling scheme is not an e-variable, as the expectation under the null hypothesis with Poisson distributions on individual cell counts exceeds 1 for rates $\lambda \geq 1$:

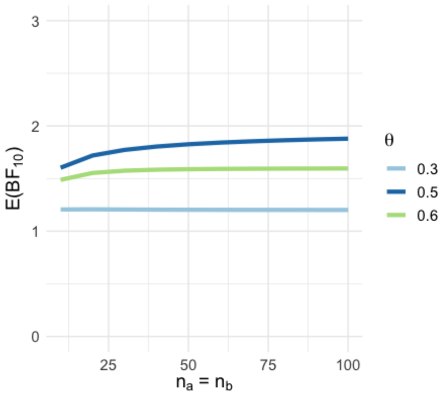
$$\mathbb{E}_{n_{rc} \sim \text{Poisson}(\lambda_{rc})} \left[BF_{10}(N_{a1}, N_{b1}, N_{a0}, N_{b0}) \right] =$$
$$\sum_{n_{a1}=0}^{\infty} \cdots \sum_{n_{b0}=0}^{\infty} \pi_{\lambda_{a1}}(n_{a1}) \ldots \pi_{\lambda_{b0}}(n_{b0}) BF_{10}(n_{a1}, n_{b1}, n_{a0}, n_{b0}) =$$
$$\frac{8}{\exp(\lambda_{a1} + \ldots + \lambda_{b0})} \sum_{n_{a1}=0}^{\infty} \cdots \sum_{n_{b0}=0}^{\infty} \lambda_{a1}^{n_{a1}} \ldots \lambda_{b0}^{n_{b0}} \frac{(n+1)(n_1+1)}{(n+4)(n+2)} \frac{n!}{(n_1+1)! n_0! n_a! n_b!},$$

as illustrated numerically in Figure S2.1 for increasing limits for the sums $\sum_{n_{rc}=1}^{\max n_{rc}}$.

For the independent multinomial sampling scheme, let, without loss of gener-



(a) The Gunel-Dickey Bayes factor for the Poisson sampling scheme is not an e-variable: $\sum_{n_{a1}=0}^{\max n_{rc}} \ldots \sum_{n_{b0}=0}^{\max n_{rc}} \pi_{\lambda_{a1}}(n_{a1}) \ldots \pi_{\lambda_{b0}}(n_{b0})$ $BF_{10}(n_{a1}, n_{b1}, n_{a0}, n_{b0})$ for various $\max n_{rc}$ and λ_{rc}.



(b) The Gunel-Dickey Bayes factor for the independent multinominal sampling scheme is not an e-variable: $\mathbb{E}_{N_{a1}, N_{b1} \sim \text{Binomial}(\theta)} [BF_{10}(N_{a1}, N_{b1} | n_a, n_b)]$ for various choices of θ and n_g.

Figure S2.1: GD

ality, $n_a < n_b$. We get, with $n_0 = n - n_1$,

$$\mathbb{E}_{N_{a1}, N_{b1} \sim \text{Binomial}(\theta)} \left[BF_{10}(N_{a1}, N_{b1} | n_a, n_b) \right] =$$
$$\sum_{n_{a1}=0}^{n_a} \sum_{n_{b1}=0}^{n_b} \binom{n_a}{n_{a1}} \binom{n_b}{n_{b1}} \theta^{n_1} (1-\theta)^{n_0} \frac{\binom{n}{n_1}}{\binom{n_a}{n_{a1}}\binom{n_b}{n_{b1}}} \frac{(n+1)}{(n_a+1)(n_b+1)} =$$
$$\frac{(n+1)}{(n_a+1)(n_b+1)} \sum_{n_{a1}=0}^{n_a} \sum_{n_{b1}=0}^{n_b} \binom{n}{n_1} \theta^{n_1} (1-\theta)^{n_0}$$

Numerical simulations show that, for a range of choices for n, n_a and θ this exceeds 1; see Figure S2.1.

S2.D Type-I error guarantee under optional stopping

Type-I Error In Figure S2.2 type-I error rates of several e-variables and Fisher's exact test estimated through a simulation experiment are depicted. 2000 samples of length 1000 were drawn according to a Bernoulli(0.1) distribution to represent 1000 data streams in two groups. After each complete block $m \in \{1, \ldots, 1000\}$ an e-value or p-value was calculated and the proportion of rejected experiments up until m with each test type was recorded. As the stream lengths increase, the type-I error rate under (incorrectly applied) optional stopping with Fisher's exact test increases quickly. The type-I error rate of the e-variables remains bounded.

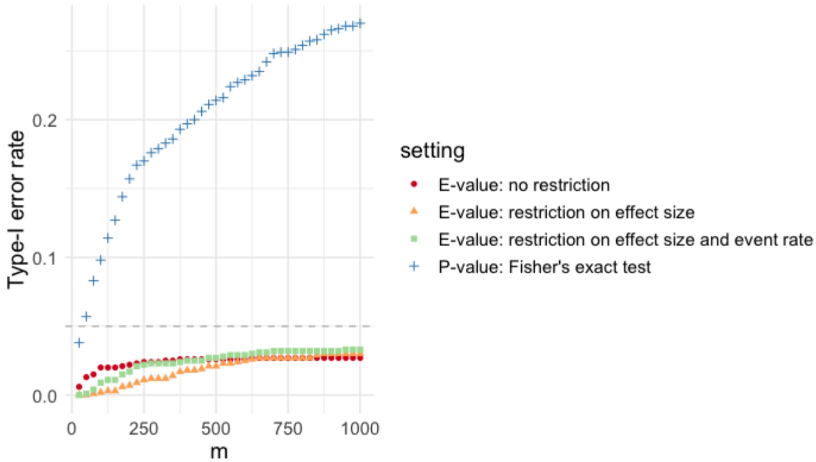


Figure S2.2: Type-I error rates for various e-variables and Fisher's exact test under optional stopping estimated with 1000 simulations of two Bernoulli(0.1) data streams of length 1000, with $n_a = n_b = 1$. Significance level $\alpha = 0.05$ was used (grey dashed line). For the safe tests, beta prior parameter values used were $\gamma = \alpha_a = \beta_a = \alpha_b = \beta_b = 1/2$ ($\gamma = 0.18$ gave comparable results). For the e-variables with restrictions on $\mathcal{H}_1$, we used $\delta = 0.05$ and $\theta_a = 0.1$.

S2.E Adjusting n_a and n_b based on past data

To see how to choose n_a and n_b for subsequent blocks based on past data, we first need to formalize the fact that data in different streams may arrive asynchronously. Thus, let $t = 1, 2, \ldots$ represent global ('calendar') time, and introduce corresponding random variables V_t and G_t: at each t, we obtain an outcome V_t in $\mathcal{Y}$ in group $G_t \in \{a, b\}$. We make no assumptions about the relative ordering of outcomes from the two groups. At time t, we have that t_a, the number of a's that are observed so far, and t_b, the number of b's observed so far, satisfy $t_a + t_b = t$, but subject to this constraint we allow them coming in any order. We now introduce a function $f : \bigcup_{t \geq 0} \mathcal{Y}^t \times \{0,1\}^t \rightarrow \{\text{STOP-BLOCK}, \text{CONTINUE}\}$ that, at each point in time t, decides whether the current block should end ($f(V^t, G^t) = $ STOP-BLOCK) or not ($f(V^t, G^t) = $ CONTINUE). As long as the value of this function does not depend on the actual outcomes V_t observed after the last block that was completed, all requirements for having a test martingale and thus for safe optional stopping are met. For example, suppose that on data $V_1, G_1, V_2, G_2, \ldots, V_t, G_t$ observed so-far, f has output STOP-BLOCK at m occasions, the last time at $t' = t - k$ for some $k > 0$. Then $f(t)$ is allowed to depend on $Y^{(m)}$ and G^t, but for any fixed $Y^{(m)} = y^{(m)}, G^t = g^t$, for all $y^k, y'^k \in \mathcal{Y}^k$, we must have $f((y^{(m)}, y^k), g^t) = f((y^{(m)}, y'^k), g^t)$.

Supplementary material for chapter 3

Appendix section S3.A contains proofs and section S3.B contains extended simulation results.

S3.A Proofs

Both proofs below use Theorem 1 of Grünwald et al. [2022a] and a direct corollary (called Corollary 2 by Grünwald et al. [2022a]), which we re-state here, for convenience, combined as a single statement. Recall that we use notation $P_W := \int P_{\vec{\theta}} dW(\vec{\theta})$.

Theorem (Theorem 1 of Grünwald et al. [2022a]) Let Y be a random variable taking values in a set $\mathcal{Y}$. Suppose Q is a probability distribution for Y with density q that is strictly positive on all of $\mathcal{Y}$ and let $\mathcal{H}_0 = \{P_{\vec{\theta}} : \vec{\theta} \in \vec{\Theta}_0\}$ be a set of distributions for Y where each $P_{\vec{\theta}}$ has density $p_{\vec{\theta}}$. Let $\mathcal{W}_0$ be the set of all distributions on $\vec{\Theta}_0$. Assume $\inf_{W_0 \in \mathcal{W}_0(\vec{\Theta}_0)} D(Q \| P_{W_0}) < \infty$. Then (a) there exists a (potentially sub-) distribution P_0^* with density p_0^* such that

$$S^* := \frac{q(Y)}{p_0^*(Y)}$$

is an e-variable (p_0^* is called the *Reverse Information Projection (RIPr) of q onto $\{p_W : W \in \mathcal{W}_0\}$*). Moreover, (b), S^* satisfies

$$\sup_{S \in \mathcal{E}(\vec{\Theta}_0)} \mathbf{E}_{Y \sim Q}[\log S] = \mathbf{E}_{Y \sim Q}[\log S^*] = \inf_{W_0 \in \mathcal{W}_0(\vec{\Theta}_0)} D(Q \| P_{W_0}) = D(Q \| P_0^*). \tag{A.5}$$

(where $\mathcal{E}(\vec{\Theta}_0)$ is the set of all e-variables relative to null hypothesis $\mathcal{H}_0$) and S^* is thus the Q-GRO e-variable for Y. If the minimum is achieved by some W_0^*, i.e. $D(Q\|P_0^*) = D(Q\|P_{W_0^*})$, then $P_0^* = P_{W_0^*}$. Moreover, (c), if there exists an e-variable S of the form $q(Y)/p_{W_0}(Y)$ for some $W_0 \in \mathcal{W}_0$ then W_0 must achieve the infimum in (A.5) and S must be essentially equal to S^* in the sense that for all $P \in \mathcal{H}_0 \cup \{Q\}$, $P(S^* = q(Y)/p_{W_0}(Y)) = 1$. Similarly (d), if there exists a $W_0^* \in \mathcal{W}_0$ that achieves the infimum in (A.5) then $S = q(Y)/p_{W_0^*}(Y)$ is an e-variable and S is again essentially equal to S^*.

Proof of Theorem 3.1 *Part 1* The real idea behind the proof is the formulation of the modified testing problem in which only a single outcome per block is observed. This we already did in the main text. Linking the two is simply the last, very simple step, with analogies to the proof of Part 1 of Theorem 1 in Turner et al. [2021].

Let $n_a, n_b \in \mathbf{N}, n := n_a + n_b$ and let $u, v \in \mathbf{R}^+$. Suppose that $n_a u + n_b v \leq n$. Then $u^{n_a} v^{n_b} \leq 1$, which follows immediately from applying Young's inequality to

$u^{n_a/n}, v^{n_b/n}$ but can also be derived directly by writing v as function of u and differentiating $\log(u^{n_a} v^{n_b})$ to u.

Further, by independence, for $(\theta_a, \theta_b) \in \vec{\Theta}_0$,

$$
\begin{aligned}
&\mathbf{E}_{Y_a^{n_a} \sim P_{\theta_a}, Y_b^{n_b} \sim P_{\theta_b}} [s'(Y_a^{n_a}, Y_b^{n_b})] = \\
&\mathbf{E}_{Y_a^{n_a} \sim P_{\theta_a}} \left[\frac{p_{\theta_a^*}(Y_a^{n_a})}{p^\circ(Y_a^{n_a}|a)} \right] \cdot \mathbf{E}_{Y_b^{n_b} \sim P_{\theta_b}} \left[\frac{p_{\theta_b^*}(Y_b^{n_b})}{p^\circ(Y_b^{n_b}|b)} \right] = \\
&\left(\mathbf{E}_{Y \sim P_{\theta_a}} \left[\frac{p_{\theta_a^*}(Y)}{p^\circ(Y|a)} \right] \right)^{n_a} \cdot \left(\mathbf{E}_{Y \sim P_{\theta_b}} \left[\frac{p_{\theta_b^*}(Y)}{p^\circ(Y|b)} \right] \right)^{n_b} = \\
&\left(\mathbf{E}_{Y \sim P'_{\vec{\theta}}|a} \left[\frac{p'_{\vec{\theta}^*}(Y|a)}{p^\circ(Y|a)} \right] \right)^{n_a} \cdot \left(\mathbf{E}_{Y \sim P'_{\vec{\theta}|b}} \left[\frac{p'_{\vec{\theta}^*}(Y|b)}{p^\circ(Y|b)} \right] \right)^{n_b} .
\end{aligned} \tag{A.6}
$$

Combining the two facts stated above, (3.6) implies that the latter quantity is bounded by 1.

Part 2 By lower-semicontinuity of the KL divergence in its second argument (Posner's theorem, used as in Grünwald et al. [2022a]) the infimum in (3.4) is achieved by some prior distribution W° so that by Theorem 1 of Grünwald et al. [2022a] (part (b) in the formulation above), $p^\circ(\cdot \mid \cdot) = p'_{W^\circ}(\cdot \mid \cdot)$ and hence also $P^\circ(G, Y) = P'_{W^\circ}(G, Y)$. By convexity of $\mathcal{H}'_0$ and finiteness of the support of $P'_{\vec{\theta}}(G, Y)$, there must be some $\vec{\theta}$ such that $P'_{W^\circ}(G, Y) = P_{\vec{\theta}}(G, Y)$ and hence also $p'_{W^\circ}(\cdot \mid \cdot) = p'_{\vec{\theta}}(\cdot \mid \cdot)$, which shows (a). This means that we have now created an e-variable for the original problem which can be written as $p_{\theta_a^*, \theta_b^*}/p_{W_0}$ with p_{W_0} a prior distribution on $\vec{\theta}_0$ (namely, the one that puts mass 1 on $\vec{\theta}$). (b) is then an immediate consequence of Theorem 1 of Grünwald et al. [2022a] (part (c) in the formulation above). (note that we *cannot* draw this conclusion if $\mathcal{H}'_0$ is not convex; for then the distribution p'_{W° may not correspond to the distribution p_{W° in the original problem — this correspondence is only guaranteed if p'_{W° coincides with some $p'_{\vec{\theta}}$.

Proof of Theorem 3.2 Recall that we assume that $\vec{\Theta}_0$ is convex and compact. We set $\text{KL}'(\theta_a, \theta_b) := D(P'_{\theta_a^*, \theta_b^*} \| P'_{\theta_a, \theta_b})$ where D is the KL divergence as in (3.5), i.e. for the modified setting in which P'_{θ_a, θ_b} is a distribution on a single outcome, as discussed before Theorem 3.1. For the 2×2 model this KL divergence can be written explicitly as

$$
\begin{aligned}
D(P'_{\theta_a^*, \theta_b^*} \| P'_{\theta_a, \theta_b}) &= \mathbf{E}_{G \sim Q'} \mathbf{E}_{Y \sim P'_{\vec{\theta}^*}|G} \left[\log \frac{p'_{\vec{\theta}^*}(Y|G)}{p'_{\vec{\theta}}(Y|G)} \right] \qquad \text{(A.7)} \\
&= \frac{n_a}{n} \mathbf{E}_{Y \sim P'_{\theta_a^*}} \left[\log \frac{p_{\theta_a^*}(Y)}{p_{\theta_a}(Y)} \right] + \frac{n_b}{n} \mathbf{E}_{Y \sim P'_{\theta_b^*}} \left[\log \frac{p_{\theta_b^*}(Y)}{p_{\theta_b}(Y)} \right] \\
&= \frac{n_a}{n} \sum_{y_a \in \{0,1\}} p_{\theta_a^*}(y_a) \log \frac{p_{\theta_a^*}(y_a)}{p_{\theta_a}(y_a)} + \frac{n_b}{n} \sum_{y_b \in \{0,1\}} p_{\theta_b^*}(y_b) \log \frac{p_{\theta_b^*}(y_b)}{p_{\theta_b}(y_b)}.
\end{aligned}
$$

From (3.8) we now see that $n\text{KL}'(\theta_a, \theta_b) = \text{KL}(\theta_a, \theta_b)$. We will prove the theorem with KL replaced by KL$'$ and $\mathcal{H}_0$ by $\mathcal{H}'_0$; since the two KL's agree up to a constant factor of n, all results transfer to the KL mentioned in the theorem statement.

Since $\vec{\Theta}_0$ is compact in the Euclidean topology and all distributions in $\mathcal{H}'_0$ can be represented as 2-dimensional vectors, i.e. they have common and finite support, we must have that $\mathcal{H}_0$ is compact in the weak topology so we can use the lower-semicontinuity of KL divergence in its second argument (Posner's theorem) as in [Grünwald et al., 2022a] to give us that the minimum KL divergence $\min \text{KL}'(\theta_a, \theta_b)$ is achieved by some $(\theta_a^\circ, \theta_b^\circ)$. Since KL divergence is strictly convex in its second argument and $\mathcal{H}'_0$ is convex (this is the place where we need to use KL$'$ rather than KL: $\mathcal{H}_0$ may *not* be convex!), the minimum must be achieved uniquely. Since KL divergence $\text{KL}'(\theta_a, \theta_b)$ is nonnegative and 0 only if $(\theta_a, \theta_b) = (\theta_a^*, \theta_b^*)$, it follows that $(\theta_a^\circ, \theta_b^\circ) = (\theta_a^*, \theta_b^*)$ if $\min \text{KL}(\theta_a, \theta_b) = 0$. Otherwise, since we assume (θ_a^*, θ_b^*) to be in the interior of $[0, 1]^2$, $\text{KL}(\theta_a, \theta_b) = \infty$ iff (θ_a, θ_b) lies on the boundary of $[0, 1]^2$. Thus, $(\theta_a^\circ, \theta_b^\circ)$ must lie in the interior of $[0, 1]^2$ as well. $(\theta_a^\circ, \theta_b^\circ)$ cannot lie in the interior of $\vec{\Theta}_0$ though: for any point (θ_a, θ_b) in the interior of $\vec{\Theta}_0$ we can draw a line segment between this point and (θ_a^*, θ_b^*). Differentiation along that line gives that $\text{KL}'(\theta_a, \theta_b)$ monotonically decreases as we move towards (θ_a^*, θ_b^*), so the minimum within the closed set $\vec{\Theta}_0$ must lie on its boundary.

It remains to show that (3.9) is the (θ_a^*, θ_b^*)-GRO e-variable relative to $\mathcal{H}_0$. To see this, note that, by convexity of $\mathcal{H}'_0$, from Theorem 3.1, we must have that the GRO e-variable for this original problem is of the form

$$\frac{p_{\theta_a^*}(y_a^{n_a}) p_{\theta_b^*}(y_b^{n_b})}{p_{\theta_a^+}(y_a^{n_a}) p_{\theta_b^+}(y_b^{n_b})}$$

for some (θ_a^+, θ_b^+). The result then follows again by Theorem 1 of Grünwald et al. [2022a] (part (c) in the formulation above): this shows that the distribution W_0 that puts mass 1 on (θ_a^+, θ_b^+) minimizes, among all distributions W on $\vec{\Theta}_0$, $D(P_{\theta_a^*, \theta_b^*} \| P_W)$. Since the set of such distributions includes all distributions that put mass 1 on *some* $(\theta_a, \theta_b) \in \vec{\Theta}_0$, we must have that $(\theta_a^+, \theta_b^+) = (\theta_a^\circ, \theta_b^\circ)$.

S3.B Extended simulation results

Numerical example We here give a small numerical example to illustrate the construction of our confidence sequences. For this example, we will look in detail at the data used to generate the second row of Figure 3.2a, the second panel, where we have observed 500 data blocks, with 27 "successes" ($y = 1$) in group a, and 136 "successes" in group b. To estimate δ_{L} and δ_{R}, $S^{(m)}_{[n_a,n_b,W_1;\vec{\Theta}_0]}$ as in (7.14) was calculated for that specific data stream, for a grid of possible δ, each defining one $\vec{\Theta}_0$; here, a grid with size 100 and a precision of 0.02 on $[-1, 1]$ was applied. The prior W_1 for the posterior mean was chosen as a Beta prior with $\alpha = \beta = 0.18$ according to Turner et al. [2021]. The area corresponding to values of δ for which $S^{(m)}_{[n_a,n_b,W_1;\vec{\Theta}_0]} < \frac{1}{0.05}$ after block $m = 500$ represents the confidence interval. For example, for the lower bound, δ_{L}, the smallest value of δ that did not lead to rejection was 0.15, with a corresponding e-value of 2.23. The e-value corresponding to $\delta = 0.13$ was 24.17, hence this risk difference was excluded from the confidence interval.

Running intersection In Figure S3.1, confidence sequence width is compared with and without applying the running intersection.

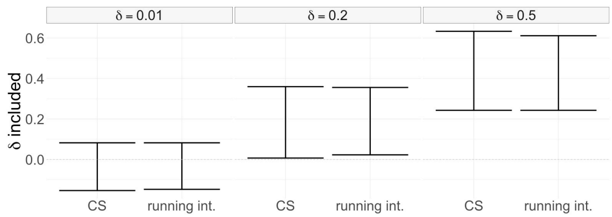


Figure S3.1: Confidence sequence with and without running intersection, for data generated under $P_{\theta_a,\theta_a+\delta}$ with $\theta_a = 0.05$, for a data stream of length 100. The significance threshold was set to 0.05. The design was balanced, with data block sizes $n_a = 1$ and $n_b = 1$.

Supplementary material for chapter 4

The following contains Section 1, *examples of theme and change phrases used for filtering sentences in the NLP pipeline*, of the supplementary material for Chapter 4 in this thesis. The other sections of the supplementary material can be found online in the publication corresponding to this chapter in *BMC Psychiatry* [Turner et al., 2022].

Table S4.1: Examples from the lists used for rule-based filtering of the four themes and change phrases

Category	**Dutch**	**Translation to English**	**Sentiment score**
Symptom reduction	Angstiger	More anxious	-1
	Angstigheid	Anxiety	-1
	Agressie	Aggression	-1
	Agresie	Aggression (misspelled)	-1
	Somber	Sad	-1
	Somer	Sad (misspelled)	-1
	Rotgevoel	Bad feeling	-1
	Doelloosheid	Aimlessness	-1
Social functioning	Zelfstandig	Independent	1
	Zelfstandige	Independent (conjugation)	1
	Zelfstandigheid	Independence	1
	Resocialiseren	Resocialize	1
	Participeert	Participates	1
	Vriendinnen	Girlfriends	1
	Vriendschappen	Friendships	1
	Verantwoordelijkheid	Responsibility	1
General well-being	Welbevinden	Well-being	1
	Welzijn	Well-being (synonym)	1
	Hoop	Hope	1
	Zingeving	Meaning	1
	Zinvol	Meaningful	1
	Zelfwaardering	Self-esteem	1
	Eigenwaarde	Self-esteem (synonym)	1
	Zelfvertrouwen	Self-confidence	1
	Zelfvetouwen	Self-confidence (misspelled)	1
Patient experience	Voelde	Felt	1
	Nez	In their own words (abbreviated)	1
	Voelt	Feels	1

Table with examples, continued

Category	**Dutch**	**Translation to English**	**Sentiment score**
	Uitte	Expressed	1
	Verwoorde	Articulated	1
	Constateert	Noted	1
	Merkt	Notes	1
	Mekrt	Notes (misspelled)	1
Change indicator	Afnam	Decreased	-1
	Afname	Decrease	-1
	Afgenomen	Decreased (conjugation)	-1
	Toenemende	Increasing	1
	Toenemde	Increasing (misspelled)	1
	Verbeter	Improve	1
	Verminder	Reduce	-1
	Vermindern	Reduce (misspelled)	-1

Supplementary material for chapter 5

Table S5.1: Overview of antidepressant prescription groups and specific antidepressants present in the data

Group	Antidepressant
MAOI	Tranylcypromine
	Moclobemide
	Phenelzine
nSSRI	Trazodone
	Duloxetine
	Venlafaxine
Other	Bupropion
	Vortioxetine
	Agomelatine
	Hyperici herba
SSRI	Sertraline
	Citalopram
	Escitalopram
	Fluoxetine
	Paroxetine
	Fluvoxamine
TetraCA	Mirtazapine
	Mianserine
TriCA	Nortriptyline
	Amitriptyline
	Clomipramine
	Imipramine
	Doxepine
	Maprotiline
	Dosulepine

Table S5.2: Overview of therapeutic dose range for selection of antidepressant treatment trajectories

antidepressant	Minimal dose	Maximal dose
tranylcypromine	10	60
phenelzine	8	120
moclobemide	100	600
clomipramine	10	250
nortriptyline	20	250
amitriptyline	10	150
imipramine	10	300

Table with dose ranges, continued

antidepressant	Minimal dose	Maximal dose
dosulepin	50	225
doxepin	25	300
trimipramine	NA	NA
venlafaxine	75	375
mirtazapine	15	45
trazodone	100	400
bupropion	150	300
duloxetine	60	120
agomelatine	25	50
vortioxetine	5	20
hyperici herba	NA	NA
sertraline	50	200
citalopram	10	40
fluoxetine	20	60
escitalopram	5	20
paroxetine	20	50
fluvoxamine	50	300

Table S5.3: Detailed summary of outcome measures per antidepressant prescription group.

AD Type	Facility	N	Continuation	Med. dur. until switch	Prescription duration	Core complaints	Social	Well-being	Experience
SSRI	PG	2244	0.680	77	162	-0.166	0.337	0.301	-0.084
	UMCU	316	0.924	16	92	-0.344	0.386	0.094	-0.217
nSSRI	PG	774	0.625	97	188	-0.174	0.324	0.302	-0.117
	UMCU	147	0.878	21	143	-0.119	0.567	0.229	-0.1128
TriCA	PG	853	0.742	86	175	-0.117	0.322	0.257	-0.077
	UMCU	192	0.901	42	122	-0.098	0.493	0.201	-0.079
TetraCA	PG	827	0.573	45	126	-0.115	0.280	0.308	-0.115
	UMCU	44	0.886	51	49	-0.182	0.689	0.140	-0.222
MAOI	PG	62	0.613	122	212	-0.102	0.167	0.250	0.101
	UMCU	45	0.733	14.5	137	-0.057	0.390	0.187	-0.121
Other	PG	224	0.558	85	170	-0.180	0.399	0.263	-0.147
	UMCU	15	0.733	14.5	54	-0.340	0.432	0.105	-0.317

Note that 171 out of 4808 trajectories at PG and 24 at UMCU concerned trajectories where two types of antidepressants were started on the same day. At PG, 106 concerned combinations of a tetracyclic antidepressant with another type; at UMCU this concerned 12 of the 24 cases. The remainder mainly consisted of combined prescriptions of tricyclic antidepressants, SSRIs and nSSRIs, possibly discontinuation schemes started at the beginning of the admission of the patient. For the outcome measure summaries in this table, if a patient started two types of antidepressants at the same day, this data is incorporated in the two separate corresponding rows in the table. This separation into two entries is offered here purely with the purpose of keeping this table concise. In the Bayesian network analyses in this manuscript, these types of trajectories are viewed as one trajectory with a combination of antidepressant types: the Bayesian network can handle learning such interactions between variables in the model.

Supplementary material for chapter 6

The supplementary material for Chapter 6 can be found online in the publication corresponding to this chapter in Psychiatry Research as: *Yuri van der Does, Rosanne J. Turner, Miel J.H. Bartels, Karin Hagoort, Aaron Metselaar, Floortje E. Scheepers, Peter D. Grünwald, Metten Somers and Edwin van Dellen. Outcome prediction of electroconvulsive therapy for depression. Psychiatry Res. 2023 Aug;326:115328. doi: 10.1016/j.psychres.2023.115328*

Supplementary material for chapter 7

Appendix section S7.A contains detailed proofs and section S7.B additional experiments and figures.

S7.A Proofs

Proof. (of theorem 7.2.1). First consider the basic case with $E^{(m)}$ as in (7.8). As we show below, we have, with $\mathbf{E} \equiv \mathbf{E}_{P_{\theta^*}}$,

$$\mathbf{E}\left[\log E^{(m)}\right] = \mathbf{E}\left[\sum_{j=1}^{m} \log S_j\right] = \mathbf{E}\left[\sum_{j=1..m}\sum_{x\in\{a,b\}}\sum_{i=1..n_x} \log \frac{p_{\breve{\theta}_{x,k_j}|Y^{(j-1)}}(Y_{j,x,i})}{p_{\breve{\theta}_{0,k_j}|Y^{(j-1)}}(Y_{j,x,i})}\right] \geq$$

$$\mathbf{E}\left[\sum_{j=1..m}\sum_{x\in\{a,b\}}\sum_{i=1..n_x} \log \frac{p_{\breve{\theta}_{x,k_j}|Y^{(j-1)}}(Y_{j,x,i})}{p_{\tilde{\theta}_{0,k_j}}(Y_{j,x,i})}\right] \geq$$

$$\mathbf{E}\left[\sum_{\substack{j=1..m\\ x\in\{a,b\}\\ i=1..n_x}} \log \frac{p_{\theta^*_{x,k_j}}(Y_{j,x,i})}{p_{\tilde{\theta}_{0,k_j}}(Y_{j,x,i})} - \sum_{\substack{k=1..K\\ x\in\{a,b\}}} \log(n_x m_k)\right] + O(1) =$$

$$\sum_{k=1..K} m_k \cdot D(P_{\theta^*_{a,k},\theta^*_{b,k}} \| P_{\tilde{\theta}_{0,k},\tilde{\theta}_{0,k}})) + O(\log m) \tag{A.8}$$

where we use notation $D(P_{\theta^*_a,\theta^*_b} \| P_{\theta_0,\theta_0})$ as in (7.4); and $\tilde{\theta}_{0,k}$ is defined as $\arg\min_{\theta\in[0,1]} D(P_{\theta^*_{a,k},\theta^*_{b,k}} \| P_{\theta,\theta})$ which by the same calculation as the one leading up to (7.4, is given by $\tilde{\theta}_{0,k} = (n_a/n)\theta^*_{a,k} + (n_b/n)\theta^*_{b,k}$, and m_k denotes the number of times that an instance of block k was observed in the first m blocks, and we remind the reader that $+O(\log m)$ may also indicate a negative difference of order $\log m$. (A.8) immediately implies the result, using (7.6).

The first two equalities in (A.8) are immediate. The first inequality follows because $P_{\tilde{\theta}_{0,k_j},\tilde{\theta}_{0,k_j}}$ minimizes KL divergence to $P_{\theta^*_{a,k_j},\theta^*_{b,k_j}}$ among all $\theta \in [0,1]$, within each block j. The final equality follows by independence and basic calculus. It remains to show the second inequality. This one follows because we use a prior $W(\theta_{a,k}, \theta_{b,k}$ under which θ_a and θ_b are independently beta distributed with strictly positive densities on $(0,1)$. We can then use a standard Laplace approximation of the Bayesian marginal likelihood to obtain, for each fixed $k \in \{1,\ldots,K\}$, where the expectation $\mathbf{E}$ is over $Y'_{(1)}, \ldots, Y'_{(m')} \sim P_{\theta^*_{a,k}, \theta^*_{b,k}}$:

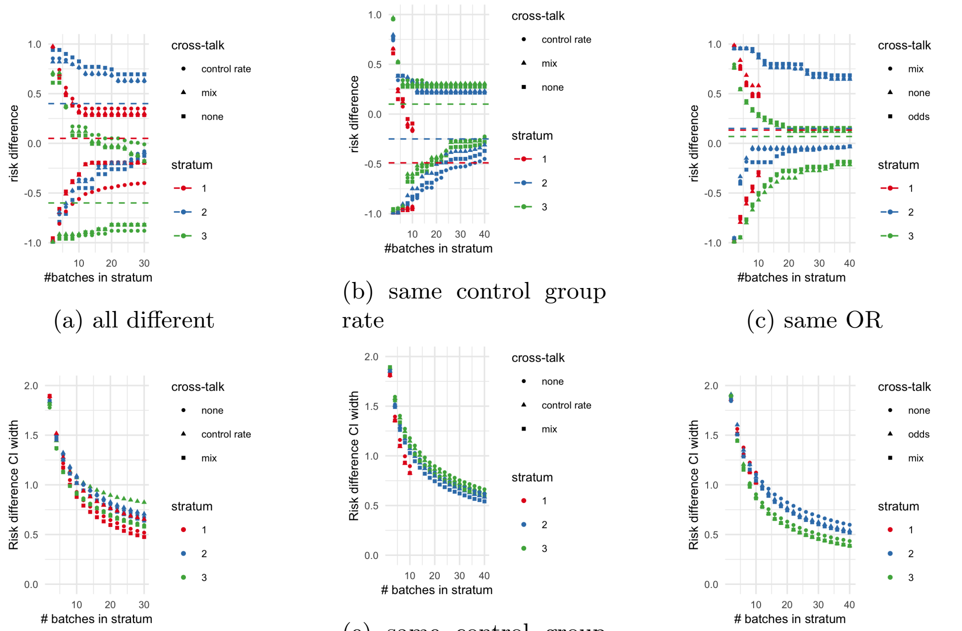
$$
\begin{aligned}
&\mathbf{E}\left[-\log \prod_{j=1}^{m'} \prod_{x \in \{a,b\}} \prod_{i=1}^{n_x} p_{\breve{\theta}_{x,k} | Y^{(j-1)}}(Y_{j,x,i}) \right] = \\
&\mathbf{E}\left[-\log \left(\int \prod_{j=1}^{m'} \prod_{x \in \{a,b\}} \prod_{i=1}^{n_x} p_{\theta_{x,k}}(Y_{j,x,i}) \right) dW(\theta_{a,k}, \theta_{b,k}) \right] \\
&\leq \mathbf{E}\left[\sum_{j=1}^{m'} -\log p_{\theta^*_{a,k}, \theta^*_{b,k}}(Y_{(j)}) \right] + \log(n_a + n_b) m' + O(1).
\end{aligned}
$$

Here the equality is standard telescoping of the Bayesian marginal likelihood, and the inequality is the Laplace approximation, i.e. the same calculation as the one leading up to the $(d/2) \log n$ BIC approximation of Bayesian marginal likelihood for a d-parameter exponential family; here $d = 2$ since we have two free parameters, $\theta^*_{a,k}$ and $\theta^*_{b,k}$; see [Grünwald, 2007, Chapter 8] for proof and detailed explanation).

This shows the result for the basic case that $E^{(m)}$ is arrived at by multiplication, (7.8). The case for $E^{(m)}_{\text{MIX}}$ follows similarly by noting that, by construction, $E^{(m)}_{\text{MIX}} \geq E^{(m)}_{\text{NONE}}/3$, where $E^{(m)}_{\text{NONE}}$ denotes the standard e-process with multiplication and without cross-talk, for which we have already (just) shown the result.

□

S7.B Additional experiments



(a) all different

(b) same control group rate

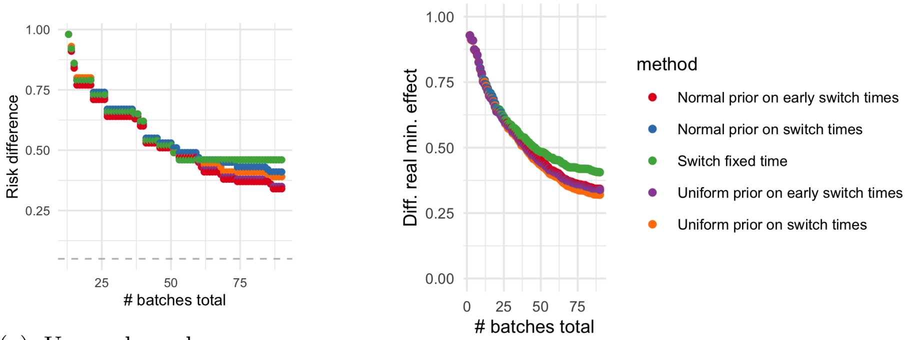
(c) same OR

(d) all different

(e) same control group rate

(f) same OR

Figure S7.1: Examples of 95% stratified confidence intervals ((a), (b) and (c)) and mean confidence interval widths estimated over 100 runs ((d), (e) and (f)) with different types of cross-talk, including mixing different types of cross-talk. In (a), (b) and (c) the true risk difference of the data generating distribution in each stratum is indicated by a dashed line. For (a) and (d), the data were generated by distributions with different control group success rates (0.1, 0.2 and 0.8) and risk differences (0.05, 0.4 and −0.6) in each stratum. For (b) and (e), strata sizes were unbalanced: as can be seen for stratum 1, the red points, data collection stopped after 10 batches. Control group success rates were all 0.5 and risk differences were different (−0.49, −0.25 and 0.1). For (c) and (f), strata sizes were unbalanced as well, and now odds ratios were the same in each stratum (2), but control group rates differed again (0.2, 0.25 and 0.85).



(a) Upper bound sequence example

(b) Average difference with true minimum

Figure S7.2: Example of a confidence sequence and average difference from upper bound to true minimal effect size value through 100 simulations, for different switch priors on j^*. 30 observations were made in each stratum, and the real differences were 0.5, 0.4 and 0.05. For the priors on early switch times, all prior mass was distributed between batch numbers 5 up to 10.α was set to 0.05.

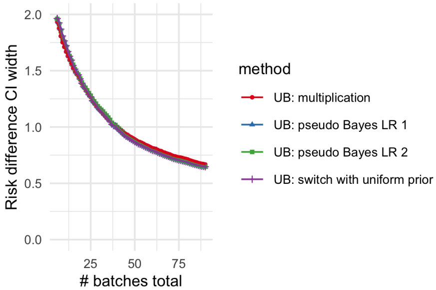
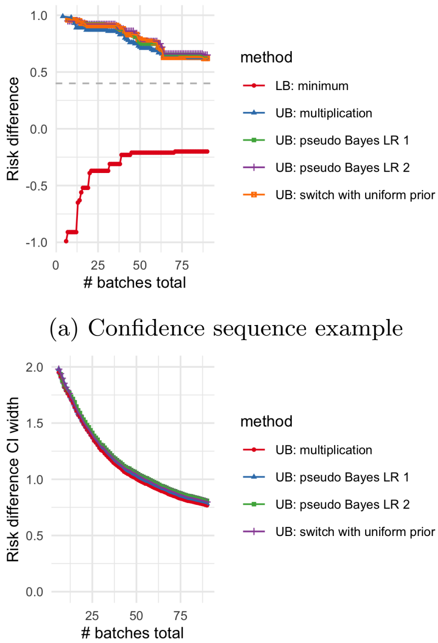


Figure S7.3: Average interval width (upper bound for the respective methods minus lower bound estimated with the minimum method) of confidence sequences for the lower- (LB) and upper (UB) bounds of the minimum effect and estimated through 100 simulations. 30 observations were made in each stratum, and the real differences were 0.5, 0.4 and 0.05. With the switch method, a uniform prior ranging from $j^* = 5$ until 30 was applied. With the pseudo-Bayesian approach, the learning rate η was set to 1 and 2. α was set to 0.05.



(a) Confidence sequence example

(b) Average width

Figure S7.4: Example of confidence sequences for the lower- (LB) and upper (UB) bounds of the minimum effect, and average interval width (upper bound for the respective methods minus lower bound estimated with the minimum method). 30 observations were made in each stratum, and the real differences were 0.4, 0.4 and 0.5. With the switch method, a uniform prior ranging from $m_{\text{switch}} = 5$ until 30 was applied. With the pseudo-Bayesian approach, the learning rate η was set to 1 and 2. α was set to 0.05.

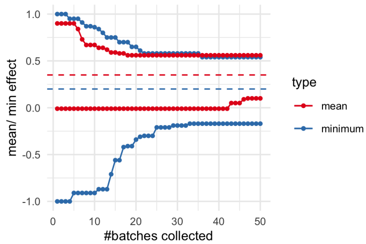


Figure S7.5: Simulated example of a confidence sequence for the mean effect across subpopulations. 25 observations were made in each stratum, and the real risk differences were 0.2 and 0.5. The confidence sequence for the mean difference is plotted alongside the confidence sequence for the minimum of the differences, estimated with pseudo-Bayesian averaging and a uniform switch prior. α was set to 0.05.