Supplementary Materials for "Simultaneous Confidence Intervals Compatible with Sequentially Rejective Graphical Procedures" in *Statistics in Biopharmaceutical Research* by Olivier J. M. Guilbaud

### Appendix A: Detailed Illustration with a Fallback MTP, cf. Section 4.3.3

We illustrate Algorithm 1 and the bounds (20) with the Fallback MTP that has default graph in Figure 1(b) with  $v_1 = 1/2$ ,  $v_2 = v_3 = 1/4$ , and  $\alpha = 0.025$ , using the same data as in Guilbaud (2009, sec. 3.1.3). These sequence weights  $v_1, v_2, v_3$  correspond to the choice  $w_1 = 1/2$  and  $w_2 = w_3 = 1/4$  of *a priori* weights discussed at the end of Example 2. The data come from a study reported by Hartung et al. (2002) in which two doses of mitoxandrone were compared with placebo in multiple-sclerosis patients with respect to five primary efficacy variables (originally through a Fixed-Sequence MTP).

For our illustration we consider only the high-dose vs. placebo comparison with respect to the first three primary efficacy variables, as in Guilbaud (2009, sec. 3.1.3). Briefly, these three variables are, in relevant order:  $Y_1 =$  (change from baseline of expanded disability status scale),  $Y_2 =$  (change from baseline of ambulation index), and  $Y_3 =$  (number of relapses treated with corticosteroids). For each i = 1, 2, 3, the comparison was in terms of the quantity  $\theta_i = \Pr[Y_i' > Y_i''] - \Pr[Y_i' < Y_i'']$ , where  $Y_i'$  and  $Y_i''$  denote independent random  $Y_i$ -variables from underlying patient populations treated with placebo and active dose, respectively; and the aim was to show that  $\theta_i > 0$ , i.e. to reject the null hypothesis that  $\theta_i \leq 0$ . This is thus in accordance with the setup in Section 2, with hypotheses  $H_i$  in (1) that have target/boundary values  $\theta_{i,0} = 0$ .

The observed values of  $\hat{\theta}_i$ ,  $se_i$ , and  $p_i$  are based on large-sample marginal two-sided 95% confidence intervals of the form  $\hat{\theta}_i \pm 1.96 se_i$  reported by Hartung et al. (2002); see Guilbaud (2009, section 3.1.3) for details. The subsequent inferences based on these observed values are approximate (the underlying asymptotic argument amounts to pretending that each  $(\hat{\theta}_i - \theta_i)/se_i \sim \mathcal{N}(0, 1)$  and that each  $se_i$ -value is a known constant). The observed values of  $\hat{\theta}_i$ ,  $se_i$ , and  $p_i$  are given in Table A.1 for Outcome Scenario 1. Another Outcome Scenario 2 is also given in Table A.1 where the  $\hat{\theta}_1$ -value has been increased and the  $\hat{\theta}_2$ -value has been decreased, to illustrate what happens with another  $\mathcal{R}$ outcome. These outcome scenarios are the same as in Guilbaud (2009, table 3) where alternative confidence bounds were considered. These two scenarios were also used by Schmidt and Brannath (2015, tables 1 and 2).

Now, consider Outcome Scenario 1. We first verify that Algorithm 1 rejects all hypotheses  $H_1, H_2, H_3$ . For simplicity we may consider the informal description of this algorithm given in the third paragraph of Section 3. In the first step of the algorithm, both  $H_1$  and  $H_3$  are rejected because  $p_1 \le \alpha v_1 =$ 0.025(1/2) and  $p_3 \le \alpha v_3 = 0.025(1/4)$ , whereas  $H_2$  is not rejected because  $p_2 > \alpha v_2 =$ 0.025(1/4). However, in the second step, also  $H_2$  becomes rejected because  $p_2 \le \alpha (v_1 + v_2) =$ 0.025(1/2 + 1/4). Thus,  $\mathcal{R} = \{1, 2, 3\}$  in this scenario. It then follows from (19) and (20) that  $\tilde{L}_i = \theta_{i,0} \vee p_i^{-1}(\underline{\alpha}_i)$  for i = 1, 2, 3; because all three sequences in Figure 1(b) have been entirely rejected. Here  $\theta_{i,0} = 0$ ,  $\underline{\alpha}_i = \alpha v_i$ , and we have from (8) that  $p_i^{-1}(u) = \hat{\theta}_i - \Phi^{-1}(1-u) se_i$ ; which leads to the lower confidence bounds  $\tilde{L}_1, \tilde{L}_2, \tilde{L}_3$  given in the last row of Table A.1 for Outcome Scenario 1. Note that the relations  $\tilde{L}_1 > \theta_{1,0}, \tilde{L}_2 = \theta_{2,0}, \tilde{L}_3 > \theta_{3,0}$ , are in accordance with the facts that  $p_1 \equiv p_1(\theta_{1,0}) \leq \alpha v_1, p_2 \equiv p_2(\theta_{2,0}) > \alpha v_2, p_3 \equiv p_3(\theta_{3,0}) \leq \alpha v_3$ , respectively. In particular, note that although  $\mathcal{R} = \{1, 2, 3\}$ , the assertion " $\tilde{L}_2 < \theta_2$ " about  $\theta_2$  is not sharper than the rejection assertion " $\theta_{2,0} < \theta_2$ ".

Next, consider Outcome Scenario 2. We first verify that Algorithm 1 rejects  $H_1$  and  $H_3$ , but not  $H_2$ . In the first step of the algorithm, both  $H_1$  and  $H_3$  are rejected because  $p_1 \le \alpha v_1 = 0.025(1/2)$  and  $p_3 \le \alpha v_3 = 0.025(1/4)$ , whereas  $H_2$  is not rejected because  $p_2 > \alpha v_2 = 0.025(1/4)$ , as in Outcome Scenario 1. However, in contrast to Outcome Scenario 1, the hypothesis  $H_2$  is not rejected in the second step, because  $p_2 > \alpha (v_1 + v_2) = 0.025(1/2 + 1/4)$ . Thus,  $\mathcal{R} = \{1, 3\}$  in this scenario.

It then follows from (19) and (20) that  $\tilde{L}_1 = \theta_{1,0} \vee p_1^{-1}(\underline{\alpha}_1)$ ,  $\tilde{L}_2 = p_2^{-1}(\alpha_2(\mathcal{R}))$ , and  $\tilde{L}_3 = \theta_{3,0} \vee p_3^{-1}(\underline{\alpha}_3)$ . Here  $\theta_{i,0} = 0$ ,  $\underline{\alpha}_1 = 0$ ,  $\alpha_2(\mathcal{R}) = \alpha(v_1 + v_2)$ , and  $\underline{\alpha}_3 = \alpha v_3$ , because  $S_1$  is not entirely rejected,  $H_2$  in  $S_2$  is not rejected, and  $S_3$  is entirely rejected; and  $p_i^{-1}(u) = \hat{\theta}_i - \Phi^{-1}(1-u) se_i$ ; which leads to the lower bounds  $\tilde{L}_1, \tilde{L}_2, \tilde{L}_3$  given in the last row of Table A.1 for Outcome Scenario 2. Note that the relations  $\tilde{L}_1 = \theta_{1,0}, \tilde{L}_2 < \theta_{2,0}, \tilde{L}_3 > \theta_{3,0}$ , are in accordance with the facts that  $p_1^{-1}(0) = -\infty$ ,  $p_2 \equiv p_2(\theta_{2,0}) > \alpha(v_1 + v_2)$ ,  $p_3 \equiv p_3(\theta_{3,0}) \le \alpha v_3$ , respectively.

**Table A.1** Quantities involved in simultaneous  $1 - \alpha$  confidence bounds  $\tilde{L}_1, \tilde{L}_2, \tilde{L}_3$  given by (20) for  $\theta_1, \theta_2, \theta_3$  based on the default graph in Figure 1(b) with  $v_1 = 1/2$ ,  $v_2 = v_3 = 1/4$ , and  $\alpha = 0.025$ , under two outcome scenarios, where  $\mathcal{R} = \{1, 2, 3\}$  and  $\mathcal{R} = \{1, 3\}$  under Outcome Scenario 1 and 2, respectively.

	Outcome Scenario 1			Outcome Scenario 2		
Quantity	<i>i</i> = 1	<i>i</i> = 2	<i>i</i> = 3	<i>i</i> = 1	<i>i</i> = 2	<i>i</i> = 3
$ heta_{i,0}$	0	0	0	0	0	0
$\widehat{ heta}_i$	0.240	0.210	0.385	0.300	0.190	0.385
se <sub>i</sub>	0.102	0.097	0.105	0.102	0.097	0.105
$p_i$	0.0093	0.0151	0.0001	0.0016	0.0250	0.0001
$H_i$ rejected?	Yes	Yes	Yes	Yes	No	Yes
$\tilde{L}_i$	0.011	0	0.124	0	-0.012	0.124

Finally, we note from Section 4.3.3 that if in another Outcome Scenario, the last hypothesis  $H_3$  is not rejected, then the confidence bound  $\tilde{L}_i$  of any rejected hypothesis  $H_i$  with i < 3 is necessarily equal to  $\theta_{i,0}$ , i.e. not larger/sharper than  $\theta_{i,0}$ , even if the  $p_i$ -value is extremely small. As shown in Remark 6, the last hypothesis in the given sequence of hypotheses has this crucial role not only for the particular confidence bounds (20) or their equivalent version (22), but also for any alternative confidence bounds based on Strassburger and Bretz (2008, eq. (8)) for a Fallback MTP.

### Appendix B: Comparisons of Confidence Bounds for a Fallback MTP, cf. Section 4.3.3

Consider the Original Fallback MTP with default graph shown in Figure 1(b) that has K = m = 3 sequences  $S_k$  with weights  $v_k$  equal to the *a priori* weights  $w_k$ . This MTP was discussed in Examples 2 and 4, and some results concerning confidence bounds were mentioned in Section 4.3.3 and Remark 6. This MTP was also used for the illustration in Appendix A. In the present Appendix B we compare the confidence bounds (20), with the confidence bounds based on the expression in Dmitrienko et al. (2009, p. 72). The latter bounds are valid for the special case with equal *a priori* weights  $w_i = 1/m$ . Therefore, in order to illustrate and discuss differences between these two sets of confidence bounds, we *assume in the remaining part of this Appendix* that m = 3 and  $w_1 = w_2 = w_3 = 1/3$ , so that  $v_1 = v_2 = v_3 = 1/3$  in Figure 1(b).

Guilbaud (2009, sec. 3) discussed alternative confidence bounds that can take advantage of the fact that the Fallback MTP is not  $\alpha$ -exhaustive. In the particular situation considered here, we let

$$\mathcal{L}_{1}^{(x)}, \mathcal{L}_{2}^{(x)}, \mathcal{L}_{3}^{(x)},$$
 (B.1)

denote a set of such alternative lower confidence bounds for  $\theta_1, \theta_2, \theta_3$ , where x is a pre-specified parameter that can assume any value in the interval [0, 1/3]. There are thus infinitely many sets of compatible confidence bounds (B.1) indexed by  $x \in [0, 1/3]$  even for this simple Fallback MTP. We do not go into details about all these alternative bounds, except to say that their description and determination is far from simple and transparent (they can be obtained from Guilbaud (2009, table 2) with  $w'_1 = w'_2 = w'_3 = 1/3$  and any given  $0 \le x \le 1/3$ ).

It turns out that the confidence bounds (20) and the Dmitrienko et al. (2009, p.72) confidence bounds are special cases of the bounds (B.1). More precisely, the Dmitrienko et al. (2009, p. 72) bounds correspond to the parameter value x = 1/6; whereas the bounds (20) correspond to the parameter value x = 1/3. It also turns out that these two sets of bounds are equal for all outcomes of the rejection-index set  $\mathcal{R}$ , except for  $\mathcal{R} = \{3\}$  and  $\mathcal{R} = \{1, 3\}$ . To illustrate and discuss differences, we therefore only have to consider these two  $\mathcal{R}$ -outcomes. Consider first the outcome  $\mathcal{R} = \{3\}$ , i.e. the outcome  $p_1 > \alpha/3$ ,  $p_2 > \alpha/3$ , and  $p_3 \le \alpha/3$ . In this case, the (x = 1/6)-bounds of Dmitrienko et al. (2009, p. 72) and the (x = 1/3)-bounds (20) for  $\theta_1, \theta_2, \theta_3$  are

$$p_1^{-1}(\alpha/3), \ p_2^{-1}(\alpha/3), \ \theta_{3,0};$$
 (B.2)

$$p_1^{-1}(\alpha/3), \ p_2^{-1}(\alpha/3), \ \theta_{3,0} \lor p_3^{-1}(\alpha/3);$$
 (B.3)

respectively. Here the lower bounds  $p_1^{-1}(\alpha/3)$  and  $p_2^{-1}(\alpha/3)$  for  $\theta_1$  and  $\theta_2$  in (B.2) and (B.3) are below their critical values  $\theta_{1,0}$  and  $\theta_{2,0}$ , because  $p_1(\theta_{1,0}) > \alpha/3$  and  $p_2(\theta_{2,0}) > \alpha/3$ ; whereas the lower bound for  $\theta_3$  in (B.3) is above its critical value  $\theta_{3,0}$  (unless equality occurs in the rejection inequality  $p_3 \le \alpha/3$ ). Thus, the bounds (B.3) dominates the bounds (B.2) in that they always are at least as sharp, typically sharper.

Consider next the outcome  $\mathcal{R} = \{1, 3\}$ , i.e. the outcome  $p_1 \le \alpha/3$ ,  $p_2 > \alpha 2/3$ , and  $p_3 \le \alpha/3$ . In this case, the (x = 1/6)-bounds of Dmitrienko et al. (2009, p. 72) and the (x = 1/3)-bounds (20) for  $\theta_1, \theta_2, \theta_3$  are

$$\theta_{1,0} \vee p_1^{-1}(\alpha/6), \ p_2^{-1}(\alpha/2), \ \theta_{3,0} \vee p_3^{-1}(\alpha/6);$$
 (B.4)

$$\theta_{1,0}, p_2^{-1}(\alpha 2/3), \theta_{3,0} \vee p_3^{-1}(\alpha/3);$$
 (B.5)

respectively. Here the lower bound  $p_2^{-1}(\alpha 2/3)$  for  $\theta_2$  in (B.4) and (B.5) is below its critical value  $\theta_{2,0}$ . It can be verified that neither of the two sets (B.4) and (B.5) of bounds dominates the other, because  $p_3^{-1}(\alpha/6) < p_3^{-1}(\alpha/3)$ , and possibly also  $p_i^{-1}(\alpha/6) < \theta_{i,0}$  for i = 1 and/or i = 3.

This illustrates the difference between the Dmitrienko et al. (2009, p. 72) bounds and the bounds (20), i.e. between two of the many alternative sets of bounds (B.1) indexed by  $x \in [0, 1/3]$ .

# Appendix C: Direct Proof that $\tilde{L}_1, \dots, \tilde{L}_m$ Satisfy Inequality (21)

## C.1 Idea Behind the Direct Proof

Let *T* be the unknown subset of  $M \equiv \{1, ..., m\}$  that consists of the indexes *i* of the hypotheses  $H_i$  which are true. The complementary set  $M \setminus T$  then consists of the indexes *i* of the hypotheses  $H_i$  which are false. The subsequent developments are as if the sets *T* and  $M \setminus T$  are both non-empty, but the modifications in case one of these two sets is empty are straightforwards. Note that Algorithm 1 makes no erroneous rejection (of a true hypothesis) if and only if  $\mathcal{R} \subset M \setminus T$ .

For each non-empty set  $\mathcal{D} \subset M$ , let  $\underline{\alpha}_1(\mathcal{D}), \dots, \underline{\alpha}_m(\mathcal{D})$  be the  $\alpha$ -fractions defined by

$$\underline{\alpha}_{i}(\mathcal{D}) = \alpha \times \begin{pmatrix} \text{sum of weights } v_{k} \text{ over indexes } k \text{ of sequences } \mathcal{S}_{k} \text{ for} \\ \text{which } H_{i} \text{ is the first hypothesis and } I(\mathcal{S}_{k}) \subset \mathcal{D} \end{pmatrix};$$
(C.1)

where  $I(S_k)$  denotes the set of indexes of the hypotheses in sequence  $S_k$ , and the right-hand side of (C.1) is defined as zero if there is no  $S_k$  for which  $H_i$  is the first hypothesis and  $I(S_k) \subset \mathcal{D}$ . In particular,  $\underline{\alpha}_i(\mathcal{D}) = 0$  if  $i \in M \setminus \mathcal{D}$ . These  $\alpha$ -fractions are monotonic in  $\mathcal{D}$  in that,

$$\underline{\alpha}_i(\mathcal{D}') \le \underline{\alpha}_i(\mathcal{D}'') \text{ if } i \in \mathcal{D}' \subset \mathcal{D}'' \subset M.$$
(C.2)

This monotonicity can be verified as follows. Let  $\kappa_i(\mathcal{D})$  denote the set of indexes k over which the sum in (C.1) is taken. Suppose that  $i \in \mathcal{D}' \subset \mathcal{D}'' \subset M$  are given. We then have the relation  $\kappa_i(\mathcal{D}') \subset \kappa_i(\mathcal{D}'')$ , because  $I(\mathcal{S}_k) \subset \mathcal{D}' \Rightarrow I(\mathcal{S}_k) \subset \mathcal{D}''$ ; and therefore the sum of weights  $v_k$  over  $k \in \kappa_i(\mathcal{D}')$  is at most as large as over  $k \in \kappa_i(\mathcal{D}'')$ .

The confidence bounds  $\tilde{L}_1, \dots, \tilde{L}_m$  given by (20) can then be expressed as,

$$\tilde{L}_{i} = \begin{cases} \theta_{i,0} \lor p_{i}^{-1}(\underline{\alpha}_{i}(\mathcal{R})), & \text{if } i \in \mathcal{R}, \\ p_{i}^{-1}(\alpha_{i}(\mathcal{R})), & \text{if } i \in M \backslash \mathcal{R}, \end{cases}$$
(C.3)

in terms of the  $\alpha$ -fractions  $\underline{\alpha}_i(\mathcal{R})$  and  $\alpha_i(\mathcal{R})$  given by (C.1) and (10).

The idea behind the proof of inequality (21) is to compare the bounds  $\tilde{L}_1, ..., \tilde{L}_m$  with the unobervable bounds  $\tilde{L}_1^*, ..., \tilde{L}_m^*$  given by

$$\tilde{L}_{i}^{*} = \begin{cases} \theta_{i,0} \vee p_{i}^{-1} \left( \underline{\alpha}_{i}(M \setminus T) \right), & \text{if } i \in M \setminus T, \\ p_{i}^{-1} \left( \alpha_{i}(M \setminus T) \right), & \text{if } i \in T, \end{cases}$$
(C.4)

and: (a) show that the unobservable bounds  $\tilde{L}_i^*$  have simultaneous coverage probability satisfying

$$\Pr[\tilde{L}_i^* < \theta_i \text{ for all } i \in M] \ge 1 - \alpha ; \tag{C.5}$$

and (b) show that if a coverage error is made with the bounds  $\tilde{L}_i$ , then a coverage error is made with the unobservable bounds  $\tilde{L}_i^*$ , i.e. show the relation

$$[\theta_i \le \tilde{L}_i \text{ for some } i \in M] \subset [\theta_i \le \tilde{L}_i^* \text{ for some } i \in M]$$
(C.6)

between non-coverage events. It follows from relations (C.5) and (C.6) by considering complementary events that the bounds  $\tilde{L}_i$  have simultaneous coverage probability satisfying

$$\Pr[\tilde{L}_i < \theta_i \text{ for all } i \in M] \ge 1 - \alpha . \tag{C.7}$$

We therefore only have to show the relations (C.5) and (C.6). This is done in the next two sections. It may be noted that this proof of (21) is direct in that it is essentially based on the monotonicity relations (13) and (C.2); that is, it does not involve closed-testing or partitioning arguments.

## C.2 Proof that the Unobservable Bounds $\tilde{L}_1^*$ , ..., $\tilde{L}_m^*$ Satisfy Inequality (C.5)

The simplifying aspect of the lower bounds  $\tilde{L}_i^*$  given by (C.4) is that they do not involve the rejection index-set  $\mathcal{R}$  which is random. Clearly, the non-coverage event to the right of  $\subset$  in (C.6) is equal to the union of the two events  $E_1 = [\theta_i \leq \tilde{L}_i^*$  for some  $i \in M \setminus T]$  and  $E_2 = [\theta_i \leq \tilde{L}_i^*$  for some  $i \in T]$ . We consider these two events  $E_1$  and  $E_2$  separately in the next two subsections.

*C.2.1 The Event*  $E_1$ . Let us first consider the event  $E_1$  which equals the union over  $i \in M \setminus T$  of the events  $[\theta_i \leq \tilde{L}_i^*]$ . The following sequence of relations for the probability  $Pr(E_1)$  can be verified using (C.4):

$$Pr(E_{1}) = Pr\left(\bigcup_{i \in M \setminus T} \left[\theta_{i} \leq \theta_{i,0} \lor p_{i}^{-1}\left(\underline{\alpha}_{i}(M \setminus T)\right)\right]\right),$$
  
$$= Pr\left(\bigcup_{i \in M \setminus T} \left[\theta_{i} \leq p_{i}^{-1}\left(\underline{\alpha}_{i}(M \setminus T)\right)\right]\right),$$
  
$$\leq \sum_{i \in M \setminus T} Pr\left(\left[\theta_{i} \leq p_{i}^{-1}\left(\underline{\alpha}_{i}(M \setminus T)\right)\right]\right),$$
  
$$\leq \sum_{i \in M \setminus T} \underline{\alpha}_{i}(M \setminus T).$$
  
(C.8)

Here: the equality sign = in the second row follows from the fact that  $\theta_{i,0} < \theta_i$  for each  $i \in M \setminus T$ , because each  $H_i$  with  $i \in M \setminus T$  is false; the inequality sign  $\leq$  at the beginning of the third row follows from Boole's inequality; and the inequality sign  $\leq$  in the fourth row follows from (4). Now, it follows from expression (C.1) with  $\mathcal{D} = M \setminus T$  that each original sequence  $S_k$  with  $I(S_k) \subset M \setminus T$  contributes with its weight  $v_k$  to the last sum in (C.8), and that

$$\Pr(E_1) \leq \alpha \times \begin{pmatrix} \text{sum of weights } v_k \text{ over indexes } k \text{ of sequences} \\ \mathcal{S}_k \text{ for which } I(\mathcal{S}_k) \subset M \setminus T \end{pmatrix}, \quad (C.9)$$

where  $I(S_k) \subset M \setminus T$  means that  $S_k$  consists only of false hypotheses.

*C.2.2 The Event*  $E_2$ . Let us next consider the event  $E_2$  which equals the union over  $i \in T$  of the events  $[\theta_i \leq \tilde{L}_i^*]$ . The following sequence of relations for the probability  $Pr(E_2)$  can then be verified using (C.4):

$$Pr(E_2) = Pr(\bigcup_{i \in T} [\theta_i \le p_i^{-1}(\alpha_i(M \setminus T))]),$$
  

$$\le \sum_{i \in T} Pr([\theta_i \le p_i^{-1}(\alpha_i(M \setminus T))]),$$
  

$$\le \sum_{i \in T} \alpha_i(M \setminus T).$$
(C.10)

Here: the inequality sign  $\leq$  at the beginning of the second row follows from Boole's inequality; and the inequality sign  $\leq$  in the third row follows from (4). Now, in the expression (10) with  $\mathcal{D} = M \setminus T$  for the  $\alpha$ -fraction  $\alpha_i(M \setminus T)$ , the  $\mathcal{D}$ -reduced sequences  $\mathcal{S}_k^{(-\mathcal{D})}$  consist of true hypotheses remaining after having deleted all false hypotheses from the original sequences. Each original sequence  $\mathcal{S}_k$  that contains at least one true hypothesis thus contributes with its weight  $v_k$  to the last sum in (C.10). It then follows from (C.10) that

$$\Pr(E_2) \leq \alpha \times \begin{pmatrix} \text{sum of weights } v_k \text{ over indexes } k \text{ of sequences} \\ \mathcal{S}_k \text{ for which } I(\mathcal{S}_k) \cap T \neq \emptyset \end{pmatrix}, \quad (C.11)$$

where  $I(S_k) \cap T \neq \emptyset$  means that  $S_k$  contains at least one true hypothesis.

*C.2.3 The Inequality (C.5).* Combining (C.9) and (C.11) we get from Boole's inequality that  $Pr(E_1 \cup E_2) \le \alpha$ ; that is, we have shown the inequality (C.5) aimed at in this section C.2.

### C.3 Proof of the Relation (C.6) Between Non-Coverage Events

In this section we show that for any outcome of the data (i.e. for any realization of random quantities) such that event to the left of  $\subset$  in (C.6) occurs, the event to the right of  $\subset$  necessarily occurs. We first consider the following two cases separately: (a) the case when the outcome of the data is such that  $\mathcal{R} \subset M \setminus T$ , i.e. when no erroneous rejection of a true hypothesis is made by Algorithm 1; and (b) the case when the outcome of the data is such that  $\mathcal{R} \cap T \neq \emptyset$ , i.e. when at least one erroneous rejection of a true hypothesis is made with Algorithm 1.

*C.3.1 The case*  $\mathcal{R} \subset M \setminus T$ . Assume that the outcome of the data is such that  $\mathcal{R} \subset M \setminus T$ . Suppose that there is an  $i \in M$  for which the non-coverage relation  $\theta_i \leq \tilde{L}_i$  occurs. Then this  $i \in M$  cannot belong to  $M \cap T^c \cap \mathcal{R}^c$ , because if it does (so that  $H_i$  is false and non-rejected), then  $\theta_{i,0} < \theta_i$  and  $\tilde{L}_i < \theta_{i,0}$ , which contradicts the inequality  $\theta_i \leq \tilde{L}_i$ . Thus the  $i \in M$  satisfies either  $i \in \mathcal{R}$  or  $i \in T$ , where  $\mathcal{R}$  and Tare disjoint. We consider these two cases separately.

Suppose first that  $i \in \mathcal{R}$  is such that  $\theta_i \leq \tilde{L}_i$ . Then because  $\mathcal{R} \subset M \setminus T$ , it follows from (C.2) that  $\underline{\alpha}_i(\mathcal{R}) \leq \underline{\alpha}_i(M \setminus T)$ . It therefore follows from the first row of (C.3) and (C.4) that the non-coverage relation  $\theta_i \leq \tilde{L}_i^*$  occurs.

Suppose instead that  $i \in T$  is such that  $\theta_i \leq \tilde{L}_i$ . Then because  $\mathcal{R} \subset M \setminus T$ , it follows from (13) that  $\alpha_i(\mathcal{R}) \leq \alpha_i(M \setminus T)$  where  $i \in M \setminus (M \setminus T) = T$ . It therefore follows from the second row of (C.3) and (C.4) that the non-coverage relation  $\theta_i \leq \tilde{L}_i^*$  occurs.

We thus have shown that if the outcome of the data is such that  $\mathcal{R} \subset M \setminus T$ , and there is an  $i \in M$  for which the non-coverage relation  $\theta_i \leq \tilde{L}_i$  occurs, then there is an  $i \in M$  for which the non-coverage relation  $\theta_i \leq \tilde{L}_i^*$  occurs.

*C.3.2 The case*  $\mathcal{R} \cap T \neq \emptyset$ . Assume that the outcome of the data is such that  $\mathcal{R} \cap T \neq \emptyset$ . There is then a first Step  $s \ge 1$  (say s =s) in Algorithm 1 in which the rejection index set  $\mathcal{R}_s$  in (15) contains at least one index *i* (say i =1) of a true hypothesis  $H_i$ ; that is, the integers s and 1 are such that

$$\mathcal{D}_{\mathbb{S}^{-1}} \subset M \setminus T; \ \mathbb{i} \in \mathcal{R}_{\mathbb{S}} \cap T; \theta_{\mathbb{i}} \le \theta_{\mathbb{i},0}; p_{\mathbb{i}} \le \alpha_{\mathbb{i}}(\mathcal{D}_{\mathbb{S}^{-1}}).$$
(C.12)

Note that the fact that  $\mathbb{1} \in \mathcal{R}_{\mathbb{S}} \cap T \subset \mathcal{R}$  implies that the non-coverage relation  $\theta_{\mathbb{I}} \leq \tilde{L}_{\mathbb{I}}$  occurs because: (a)  $\theta_{\mathbb{I}} \leq \theta_{\mathbb{I},0}$  since  $\mathbb{I} \in T$ ; and (b)  $\theta_{\mathbb{I},0} \leq \tilde{L}_{\mathbb{I}}$  according to the first row in (C.3) since  $\mathbb{I} \in \mathcal{R}$ . Now,  $p_{\mathbb{I}} \equiv p_{\mathbb{I}}(\theta_{\mathbb{I},0})$  in the last inequality  $\leq$  in (C.12), so this inequality is equivalent to  $\theta_{\mathbb{I},0} \leq p_{\mathbb{I}}^{-1}(\alpha_{\mathbb{I}}(\mathcal{D}_{\mathbb{S}-1}))$ . It then follows from this latter inequality, the first relation  $\subset$  in (C.12), and the monotonicity relation (13), that

$$\theta_{i,0} \le p_{i}^{-1} \left( \alpha_{i}(M \setminus T) \right) \text{ where } i \in T; \tag{C.13}$$

so it follows from the second row in (C.4) that the non-coverage relation  $\theta_{i} \leq \tilde{L}_{i}^{*}$  occurs.

We thus have shown that if the outcome of the data is such that  $\mathcal{R} \cap T \neq \emptyset$ , then there is an  $i \in M$  for which the non-coverage relations  $\theta_i \leq \tilde{L}_i$  and  $\theta_i \leq \tilde{L}_i^*$  occur.

C.3.3 The relation (C.6) between non-coverage events. Let  $E_{left}$  denote the  $\tilde{L}_i$ -based event to the left of  $\subset$  in (C.6), and let  $E_{right}$  denote the  $\tilde{L}_i^*$ -based event to the right of  $\subset$  in (C.6). In terms of these two non-coverage events, the results in section C.3.1 mean that

$$[\mathcal{R} \subset M \setminus T] \cap E_{\text{left}} \subset [\mathcal{R} \subset M \setminus T] \cap E_{\text{right}}; \tag{C.14}$$

that is, if the intersection event to the left of  $\subset$  occurs, then the intersection event to the right of  $\subset$  occurs. Moreover, the results in section C.3.2 mean that

$$[\mathcal{R} \cap T \neq \emptyset] \subset [\theta_i \le \tilde{L}_i \text{ and } \theta_i \le \tilde{L}_i^* \text{ for some } i \in M].$$
(C.15)

Here, the event to the right of  $\subset$  is a subset of  $E_{\text{left}}$  and a subset of  $E_{\text{right}}$ , so that

$$[\mathcal{R} \cap T \neq \emptyset] \cap E_{\text{left}} = [\mathcal{R} \cap T \neq \emptyset] = [\mathcal{R} \cap T \neq \emptyset] \cap E_{\text{right}}.$$
 (C.16)

It then follows from (C.14) and (C.16 that

$$([\mathcal{R} \subset M \setminus T] \cup [\mathcal{R} \cap T \neq \emptyset]) \cap E_{\text{left}} \subset ([\mathcal{R} \subset M \setminus T] \cup [\mathcal{R} \cap T \neq \emptyset]) \cap E_{\text{right}}.$$
(C.17)

But because  $[\mathcal{R} \subset M \setminus T] \cup [\mathcal{R} \cap T \neq \emptyset]$  is the union of two disjoint events that partition the sample space, it follows from (C.17) that  $E_{\text{left}} \subset E_{\text{right}}$ , which is the relation (C.6) aimed at in this section C.3.