Web-based Supplementary Materials for

# Fiducial Generalized Confidence Interval for Median Lethal Dose (LD50)

by

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Web Appendices are available under the Paper Information link at the Biometrics website http://www.biometrics.tibs.org.

## Web Appendix A – Simulation Procedure

In this section we describe how to use Monte Carlo simulation to set up a confidence region for $\mu$. The main simulation process is to generate a vector $\boldsymbol{u}^\star = (\boldsymbol{u}_1^\star, \ldots, \boldsymbol{u}_k^\star)$ in such a way that $Q(\boldsymbol{y}, \boldsymbol{u}^\star)$ is not empty. Then draw a sample from $Q(\boldsymbol{y}, \boldsymbol{u}^\star)$ to obtain a realization of $(\mathcal{R}_{\beta_0}, \mathcal{R}_{\beta_1})$, consequently a realization of $\mathcal{R}_\mu$. This process is repeated until the desired number of the realizations of $\mathcal{R}_\mu$ are obtained. The confidence interval of $\mu$ can be estimated based on these realizations. There are several ways to generate a $\boldsymbol{u}^\star$. Naively, one can generate $\boldsymbol{u}_1^\star$ through $\boldsymbol{u}_k^\star$ simultaneously and check if $Q(\boldsymbol{y}, \boldsymbol{u}^\star)$ is empty. If $Q(\boldsymbol{y}, \boldsymbol{u}^\star)$ is not empty, keep $\boldsymbol{u}^\star$. Otherwise, regenerate $\boldsymbol{u}^\star$. This procedure is easy to implement, but highly inefficient, especially when the number of doses, $k$, is large. To solve this problem, we use Gibbs sampling approach and generate $\boldsymbol{u}_1^\star$ through $\boldsymbol{u}_k^\star$ sequentially instead. Each component of $\boldsymbol{u}^\star$ is updated conditional on the latest values of the other components of $\boldsymbol{u}^\star$. There are $k$ components in $\boldsymbol{u}^\star$, thus $k$ steps in each iteration $t$.

Note that we do not need to generate the whole vector $\boldsymbol{u}_i^\star$. In fact all we need for finding the conditional distribution is to generate the joint distribution of

$(u^\star_{i,s_i:n_i}, u^\star_{i,s_i+1:n_i})$. For simplicity of notation, denote $(u^\star_{i,s_i:n_i}, u^\star_{i,s_i+1:n_i})$ by $(w_{i1}, w_{i2})$, $i = 1, \ldots, k$. Define

$$Q^{(t)}_{-i}(\boldsymbol{y}, \boldsymbol{u}^\star) = \Big\{(b_0, b_1)\Big| \operatorname{logit} w^{(t)}_{j1} < b_0 + b_1 x_j < \operatorname{logit} w^{(t)}_{j2}, \quad \text{for } t \geq 0,\ j = 1, \ldots, i-1,$$
$$\operatorname{logit} w^{(t-1)}_{j1} < b_0 + b_1 x_j < \operatorname{logit} w^{(t-1)}_{j2}, \quad \text{for } t \geq 1,\ j = i+1, \ldots, k\Big\},$$
$$m^{(t)}_{i1} = \min\Big(\operatorname{antilogit}(b_0 + b_1 x_i),\ (b_0, b_1) \in Q^{(t)}_{-i}(\boldsymbol{y}, \boldsymbol{u}^\star)\Big),$$

and

$$m^{(t)}_{i2} = \max\Big(\operatorname{antilogit}(b_0 + b_1 x_i),\ (b_0, b_1) \in Q^{(t)}_{-i}(\boldsymbol{y}, \boldsymbol{u}^\star)\Big).$$

The simulation proceeds as follows

For $t = 0$,

1. Generate $w^{(t)}_{i1}$ and $w^{(t)}_{i2}$, $i = 1, 2$, using the fact that $U^\star_{s_i:n_i}$ follows Beta$(s_i, n_i - s_i + 1)$ and the conditional distribution of $(1 - U^\star_{s_i+1:n_i})/(1 - U^\star_{s_i:n_i})$ given $U^\star_{s_i:n_i}$ is Beta$(n_i - s_i, 1)$. Note that if $s_i = 0$, by our definition $w^{(t)}_{i1} = 0$, only $w^{(t)}_{i2}$ is required to be generated. Likewise, if $s_i = n_i$, $w^{(t)}_{i2} = 1$ and only $w^{(t)}_{i1}$ is required to be generated.

2. From $i = 3$ through $k$,

   - if $s_i = 0$, draw $w^{(t)}_{i2}$ from truncated Beta$(1, n_i)$ with range $(m^{(t)}_{i1}, 1)$.
   - if $s_i = n_i$, draw $w^{(t)}_{i1}$ from truncated Beta$(n_i, 1)$ with range $(0, m^{(t)}_{i2})$.
   - if $0 < s_i < n_i$ and

   (a) $m^{(t)}_{i1} = 0$, draw $w^{(t)}_{i1}$ from truncated Beta$(s_i, n_i - s_i + 1)$ with range $(0, m^{(t)}_{i2})$, and draw a sample from Beta$(n_i - s_i, 1)$, denoted by $d^{(t)}_{i1}$. Then $w^{(t)}_{i2} =$

$1-(1-w_{i1}^{(t)})*d_{i1}^{(t)}$.

(b) $m_{i2}^{(t)}=1$, draw $w_{i2}^{(t)}$ from truncated Beta$(s_i+1, n_i-s_i)$ with range $(m_{i1}^{(t)},1)$, and draw a sample from Beta$(s_i,1)$, denoted by $d_{i2}^{(t)}$. Then $w_{i1}^{(t)}=w_{i2}^{(t)}*d_{i2}^{(t)}$.

(c) Otherwise, the ranges of $w_{i1}^{(t)}$ and $w_{i2}^{(t)}$ are shown in Figure 13. This is the most complicated but common case. The areas of $A$ and $B$, denoted by $\tilde{p}_1$ and $\tilde{p}_2$, can be calculated as follows

$$\begin{aligned}
\tilde{p}_1 &= \int_{m_{i1}^{(t)}}^{m_{i2}^{(t)}}\int_x^1 \frac{n_i!}{(s_i-1)!(n_i-s_i-1)!}x^{s_i-1}(1-y)^{n_i-s_i-1}dydx \\
&= B_{m_{i2}^{(t)};s_i,n_i-s_i+1} - B_{m_{i1}^{(t)};s_i,n_i-s_i+1}, \quad \text{and} \\
\tilde{p}_2 &= \int_{m_{i1}^{(t)}}^{1}\int_0^{m_{i1}^{(t)}} \frac{n_i!}{(s_i-1)!(n_i-s_i-1)!}x^{s_i-1}(1-y)^{n_i-s_i-1}dydx \\
&= \frac{n_i!}{s_i!(n_i-s_i)!}{m_{i1}^{(t)}}^{s_i}(1-m_{i1}^{(t)})^{n_i-s_i},
\end{aligned}$$

where $B_{\gamma;v_1,v_2}$ is the value of CDF of Beta$(v_1,v_2)$, evaluated at $\gamma$. In this case, one has two choices with different probability to sample $w_{i1}^{(t)}$ and $w_{i2}^{(t)}$.

i. With probability $\tilde{p}_1/(\tilde{p}_1+\tilde{p}_2)$, draw $w_{i1}^{(t)}$ from truncated Beta$(s_i, n_i-s_i+1)$ with range $(m_{i1}^{(t)}, m_{i2}^{(t)})$, and draw a sample from Beta$(n_i-s_i,1)$, denoted by $d_{i1}^{(t)}$. Then $w_{i2}^{(t)}=1-(1-w_{i1}^{(t)})*d_{i2}^{(t)}$.

ii. With probability $\tilde{p}_2/(\tilde{p}_1+\tilde{p}_2)$, draw $w_{i2}^{(t)}$ from the distribution with the probability density function given by

$$\begin{aligned}
f_Y(y) &= \int_0^{m_{i1}^{(t)}} \frac{n_i!}{\tilde{p}_2(s_i-1)!(n_i-s_i-1)!}x^{s_i-1}(1-y)^{n_i-s_i-1}I_{(m_{i1}^{(t)},m_{i2}^{(t)})}(y)dx \\
&= \frac{n_i-s_i}{(1-m_{i2}^{(t)})^{n_i-s_i}}(1-y)^{n_i-s_i-1}I_{(m_{i2}^{(t)},1)}(y),
\end{aligned}$$

and draw $w_{i1}^{(t)}$ from the distribution with the probability density function given by

$$
\begin{aligned}
f_{X|Y}(x,y) &= \frac{\frac{n_i!}{(s_i-1)!(n_i-s_i-1)!}x^{s_i-1}(1-y)^{n_i-s_i-1}I_{(0,m_{i1}^{(t)})}(x)I_{(m_{i1}^{(t)},1)}(y)}{\int_0^{m_{i1}^{(t)}}\frac{n_i!}{(s_i-1)!(n_i-s_i-1)!}x^{s_i-1}(1-y)^{n_i-s_i-1}I_{(m_{i1}^{(t)},1)}(y)dx} \\
&= \frac{s_i}{m_{i1}^{(t)\,s_i}}x^{s_i-1}I_{(0,m_{i1}^{(t)})}(x).
\end{aligned}
$$

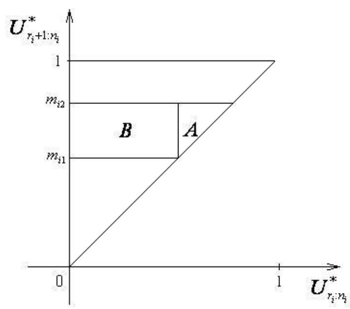


Figure 13: Illustration of case (c) in the simulation process.

For $t = 1, 2, \ldots,$ follow the same procedures as above using Step 2 for all $i = 1, \ldots, k$ to draw $(w_{i1}^{(t)}, w_{i2}^{(t)}), i = 1, \ldots, k$. At the conclusion of each cycle we compute the set

$$
Q^{(t)}(\boldsymbol{y}, \boldsymbol{w}^{(t)}) = \left\{(b_0, b_1)\,\middle|\,\operatorname{logit} w_{i1}^{(t)} < b_0 + b_1 x_i < \operatorname{logit} w_{i2}^{(t)}, \quad j = 1, \ldots, k\right\},
$$

where $\boldsymbol{w}^{(t)} = (\boldsymbol{w}_1^{(t)}, \ldots, \boldsymbol{w}_k^{(t)})$ and $\boldsymbol{w}_i^{(t)} = (w_{i1}^{(t)}, w_{i2}^{(t)}), i = 1, \ldots, k$. Note that we obtain a polygon $Q^{(t)}(\boldsymbol{y}, \boldsymbol{w}^{(t)})$ rather than a point after each iteration $t$. Thus, there are many choices to obtain a realization of $(\mathcal{R}_{\beta_0}, \mathcal{R}_{\beta_1})$, consequently a realization of $R_\mu$. For example, one can take the centroid of $Q^{(t)}(\boldsymbol{y}, \boldsymbol{w}^{(t)})$ as a realization. Based on our experience and simulation results, the best choice is to randomly select one of the vertices of $Q^{(t)}(\boldsymbol{y}, \boldsymbol{w}^{(t)})$ as a realization of $\mathcal{R}_\mu$, denoted by $\mathcal{R}_\mu^{(t)}$.

By construction process and standard theoretical results for Gibbs sampler, the generated Markov chain $\mathcal{R}_\mu^{(1)}, \mathcal{R}_\mu^{(2)}, \ldots$, converges to the fiducial generalized distribution of $\mu$.

## Web Appendix B – Proof of Theorem 1

We first compute the conditional distribution of an extremal point of (7) given it is non-empty. For simplicity of notation, set $W_{i,1} = U_{i,s_i:n_i}$ and $W_{i,2} = U_{i,s_i+1:n_i}$.

If $k = 2$, the polygon is always non-empty and has four vertices determined by one of the four sets of the equations

$$\operatorname{logit} W_{1,1} = \beta_0 + \beta_1 x_1, \quad \operatorname{logit} W_{2,1} = \beta_0 + \beta_1 x_2, \tag{8}$$

$$\operatorname{logit} W_{1,1} = \beta_0 + \beta_1 x_1, \quad \operatorname{logit} W_{2,2} = \beta_0 + \beta_1 x_2, \tag{9}$$

$$\operatorname{logit} W_{1,2} = \beta_0 + \beta_1 x_1, \quad \operatorname{logit} W_{2,1} = \beta_0 + \beta_1 x_2, \tag{10}$$

or

$$\operatorname{logit} W_{1,2} = \beta_0 + \beta_1 x_1, \quad \operatorname{logit} W_{2,2} = \beta_0 + \beta_1 x_2 \tag{11}$$

A simple calculations shows that, if $\frac{d_0 - d_1 x_1}{x_1 - x_2} > 0$ and $\frac{d_0 - d_1 x_2}{x_1 - x_2} < 0$, then (8) determines the extremal point. If $\frac{d_0 - d_1 x_1}{x_1 - x_2} < 0$ and $\frac{d_0 - d_1 x_2}{x_1 - x_2} < 0$, then (9) determines the extremal point. If $\frac{d_0 - d_1 x_1}{x_1 - x_2} > 0$ and $\frac{d_0 - d_1 x_2}{x_1 - x_2} > 0$, then (10) determines the extremal point. Finally, if $\frac{d_0 - d_1 x_1}{x_1 - x_2} < 0$ and $\frac{d_0 - d_1 x_2}{x_1 - x_2} > 0$, then (11) determines the extremal point. In the case that one of these equations is equal to 0 there is more than one extremal point. In what follows we assume that the direction $(d_0, d_1)$ was chosen in such a way that this does not happen. The density of the extremal point then is

$$g^{(d_0,d_1)}(b_0,b_1) = \frac{e^{s_1(b_0+b_1x_1)}e^{s_2(b_0+b_1x_2)}}{(1+e^{b_0+b_1x_1})^{n_1}(1+e^{b_0+b_1x_2})^{n_2}} \frac{n_1!n_2!|x_1-x_2|}{s_1!s_2!(n_1-s_1)!(n_2-s_2)!} \\ \times \frac{s_1^{1-l_{12,1}} s_2^{1-l_{12,2}} (n_1-s_1)^{l_{12,1}} (n_2-s_2)^{l_{12,2}} e^{l_{12,1}(b_0+b_1x_1)} e^{l_{12,2}(b_0+b_1x_2)}}{(1+e^{b_0+b_1x_1})(1+e^{b_0+b_1x_2})},$$

where $l_{12,\cdot}$ is either 0 or 1 depending which of the equation (8) – (11) was used.

Let $k > 2$ and the direction be chosen so that the $d_0 - d_1 x_i \neq 0$ for all $i = 1, \ldots k$. Notice that, with probability one, the extremal point happens in exactly one of the four points determined by exactly one $\binom{k}{2}$ of the pairs of double inequalities in (7). Moreover, the remaining inequalities also have to be satisfied. After some algebra we derive the conditional density of the unique extremal point to be proportional to

$$g^{(d_0,d_1)}(b_0,b_1) \propto \prod_{i=1}^{k} \left( \frac{e^{s_i(b_0+b_1x_i)}}{(1+e^{b_0+b_1x_i})^{n_i}} \right) \sum_{1\le i<j\le k} \left( \binom{n_i}{s_i}\binom{n_j}{s_j} |x_i - x_j| \right. \\ \left. \times \frac{s_i^{1-l_{ij,i}} s_j^{1-l_{ij,j}} (n_i-s_i)^{l_{ij,i}} (n_j-s_j)^{l_{ij,j}} e^{l_{ij,i}(b_0+b_1x_i)} e^{l_{ij,j}(b_0+b_1x_j)}}{(1+e^{b_0+b_1x_i})(1+e^{b_0+b_1x_j})} \right). \quad (12)$$

The rest of the proof will follow the basic ideas outlined in Hannig (2009). Set $N = n_1 + \cdots + n_k$, $\boldsymbol{S} = (S_1, \ldots, S_k)$, $\boldsymbol{n} = (n_1, \ldots, n_k)$, and recall $n_i/N \to q_i \in (0,1)$. To simplify notation set $p_i = \text{antilogit}(\beta_0 + \beta_1 x_i)$. By Central Limit Theorem,

$$\sqrt{N}\left(\frac{\boldsymbol{S}}{\boldsymbol{n}} - \boldsymbol{p}\right) \xrightarrow{\mathcal{D}} H \sim N(\boldsymbol{0}, \Sigma),$$

where $\Sigma$ is a diagonal matrix with $i^{\text{th}}$ diagonal element equal to

$$p_i(1-p_i)/r_i = \frac{1}{2r_i(1+\cosh(\beta_0+\beta_1x_i))}.$$

This verifies Assumption 1.1 of Hannig (2009).

Let $\boldsymbol{h} = (h_1, \dots, h_k)$ be a fixed vector and set $\boldsymbol{s}/\boldsymbol{n} = \boldsymbol{p} + \boldsymbol{h}/\sqrt{N} + o(N^{-1/2})$. We need to investigate the distribution of $\sqrt{N}((\mathcal{R}_{\beta_0}^{(d_0,d_1)}, \mathcal{R}_{\beta_1}^{(d_0,d_1)}) - (\beta_1, \beta_1))$. The density of this distribution is then proportional to $p(v_0, v_1) = r^{(d_0,d_1)}(\beta_0 + v_0/\sqrt{N}, \beta_1 + v_1/\sqrt{N})$. Let us now investigate the various terms that come into the definition of (12).

For simplicity of notation set

$$r_{3,(i,j)}(b_0, b_1) = \frac{s_i^{1-l_{ij,i}} s_j^{1-l_{ij,j}} (n_i - s_i)^{l_{ij,i}} (n_j - s_j)^{l_{ij,j}} e^{l_{ij,i}(b_0 + b_1 x_i)} e^{l_{ij,j}(b_0 + b_1 x_j)}}{(1 + e^{b_0 + b_1 x_i})(1 + e^{b_0 + b_1 x_j})},$$

and notice that no matter the values of $l_{ij,i}$, $0 \le N^{-2} p_3(b_0, b_1) \le 1$. Similarly set

$$r_2(b_0, b_1) = \frac{\sum_{1 \le i < j \le k} \binom{n_i}{s_i} \binom{n_j}{s_j} |x_i - x_j| r_{3,(i,j)}(b_0, b_1)}{N^2 \sum_{1 \le i < j \le k} \binom{n_i}{s_i} \binom{n_j}{s_j} |x_i - x_j|}.$$

Then again $0 \le r_2(b_0, b_1) \le 1$ and, as $N \to \infty$, $r_2(\beta_0 + v_0/\sqrt{N}, \beta_1 + v_1/\sqrt{N}) \to C_2 \in (0, 1)$. Here $C_2$ does not depend on $(v_0, v_1)$.

Finally set

$$r_1(b_0, b_1) = \prod_{i=1}^{k} \left( N^{-1/2} \binom{n_i}{s_i} \frac{e^{s_i(b_0 + b_1 x_i)}}{(1 + e^{b_0 + b_1 x_i})^{n_i}} \right).$$

By taking a log and using Taylor series we show that, as $N \to \infty$,

$$r_1(\beta_0 + v_0/\sqrt{N}, \beta_1 + v_1/\sqrt{N}) \to e^{-\sum_{i=1}^{k} \frac{q_i (v_0 + v_1 x_i)^2}{4(1 + \cosh(\beta_0 + x_i \beta_1))} + \sum_{i=1}^{k} h_i q_i (v_0 + v_1 x_i) + C_1(\mathbf{h})}. \quad (13)$$

The constant $C_1(\boldsymbol{h})$ again does not depend on $(v_1, v_2)$ and is continuous in $\boldsymbol{h}$. The function on the right-hand-side of (13) is proportional to the density of the bivariate normal distribution with variance

$$\Sigma = \begin{pmatrix} \sigma_{00} & \sigma_{10} \\ \sigma_{10} & \sigma_{11} \end{pmatrix} = \begin{pmatrix} \sum_{i=1}^{k} \frac{q_i}{2(1+\cosh(\beta_0+x_i\beta_1)} & \sum_{i=1}^{k} \frac{q_i x_i}{2(1+\cosh(\beta_0+x_i\beta_1)} \\ \sum_{i=1}^{k} \frac{q_i x_i}{2(1+\cosh(\beta_0+x_i\beta_1)} & \sum_{i=1}^{k} \frac{q_i x_i^2}{2(1+\cosh(\beta_0+x_i\beta_1)} \end{pmatrix}^{-1}$$

and mean

$$\mu(\boldsymbol{h}) = -(\sum_{i=1}^{k} h_i q_i \sigma_{00} + \sum_{i=1}^{k} h_i q_i x_i \sigma_{01}, \sum_{i=1}^{k} h_i q_i \sigma_{01} + \sum_{i=1}^{k} h_i q_i x_i \sigma_{11}).$$

A simple algebra verifies that this limiting normal distribution satisfies Assumption 1.2.b of Hannig (2009).

To verify Assumption 1.2.a, we show that $\sqrt{N}((\mathcal{R}_{\beta_0}^{(d_0,d_1)}, \mathcal{R}_{\beta_1}^{(d_0,d_1)}) - (\beta_1, \beta_1)) \xrightarrow{\mathcal{D}} N(\mu(\boldsymbol{h}), \Sigma)$. The density

$$N^{-1} g^{(d_0,d_1)} \left(\beta_0 + \frac{v_0}{\sqrt{N}}, \beta_1 + \frac{v_1}{\sqrt{N}}\right) \propto r_1 \left(\beta_0 + \frac{v_0}{\sqrt{N}}, \beta_1 + \frac{v_1}{\sqrt{N}}\right) r_2 \left(\beta_0 + \frac{v_0}{\sqrt{N}}, \beta_1 + \frac{v_1}{\sqrt{N}}\right)$$

and the right hand side converges point-wise to a constant multiple of the density of $N(\mu(\boldsymbol{h}), \Sigma)$. To show the week convergence it is enough to realize that it is also uniformly integrable. To simplify notation set $(b_0, b_1) = (\beta_0 + v_0/\sqrt{N}, \beta_1 + v_1/\sqrt{N})$. Recall that $0 \le r_2(b_0, b_1) \le 1$. Moreover, since the terms in $r_1(b_0, b_1)$ are variable changed finite multiples of beta densities. Thus we have $N^{-1/2} \binom{n_i}{s_i} \frac{e^{s_i(b_0+b_1 x_i)}}{(1+e^{b_0+b_1 x_i})^{n_i}}$ is uniformly bounded for each $i = 1, \ldots, k$, and $\prod_{i=1}^{2} \left(N^{-1/2} \binom{n_i}{s_i} \frac{e^{s_i(b_0+b_1 x_i)}}{(1+e^{b_0+b_1 x_i})^{n_i}}\right)$ is uniformly integrable. The last fact is obtained by changing variable so that we obtain a constant multiple of density of two independent beta random variables and using known facts for beta densities.

Finally we see that using Delta method we can show that the type of a confidence interval in Theorem 1 satisfies the Assumption 1.3 of Hannig (2009). The statement now follows from Theorem 1 of Hannig (2009).

# Web Appendix C – Proof of Theorem 2

If $k = 2$ the diameter of the polygon

$$\begin{aligned} D_{12} &= \operatorname{diam} Q(\boldsymbol{y}, \boldsymbol{u}^\star) \\ &= \max\left\{ \frac{\sqrt{(\Delta_1 - \Delta_2)^2 + (\Delta_1 x_2 - \Delta_2 x_1)^2}}{|x_1 - x_2|}, \frac{\sqrt{(\Delta_1 + \Delta_2)^2 + \Delta_1 x_2 + \Delta_2 x_1)^2}}{|x_1 - x_2|} \right\}, \end{aligned} \quad (14)$$

where $\Delta_i = \operatorname{logit} U_{i,s_i+1:n_i} - \operatorname{logit} U_{i,s_i:n_i}$, $i = 1, 2$. Thus, by results on spacings of uniform distribution and the delta method, $D_{12} = O_P(n^{-1})$.

Let $k \geq 3$. Since the polygon, $Q(\boldsymbol{y}, \boldsymbol{u}^\star)$ is inscribed in all of the parallelograms determined by all pairs of double inequalities in (7) we have

$$\operatorname{diam} Q(\boldsymbol{y}, \boldsymbol{u}^\star) \leq \min_{i<j} D_{ij}, \quad (15)$$

where $D_{ij}$ is defined analogously to (14). This implies that $\operatorname{diam} Q(\boldsymbol{y}, \boldsymbol{u}^\star) = O_P(N^{-1})$. Unfortunately, this is not enough as we need to prove that the conditional distribution of $\operatorname{diam} Q(\boldsymbol{y}, \boldsymbol{u}^\star) | \{\operatorname{diam} Q(\boldsymbol{y}, \boldsymbol{u}^\star) \neq \emptyset\} = O_P(N^{-1})$.

Just as in the proof in Web Appendix 7, we fix a direction $(d_0, d_1)$ such that $d_0 - d_1 x_i \neq 0$ for all $i = 1, \ldots k$. Let $E_{ij}$ denotes the event that there exist the extremal point of $Q(\boldsymbol{y}, \boldsymbol{U}^\star)$ along the direction $(d_0, d_1)$, i.e., $Q(\boldsymbol{y}, \boldsymbol{U}^\star)$ is non-empty, and it is determined by the pair of inequalities $i, j$, in (7).

Since $\{\operatorname{diam} Q(\boldsymbol{y}, \boldsymbol{u}^\star) \neq \emptyset\} = \cup_{i<j} E_{ij}$, a straightforward calculation using conditional probabilities and (15) implies that $\operatorname{diam} Q(\boldsymbol{y}, \boldsymbol{u}^\star) | \{Q(\boldsymbol{y}, \boldsymbol{u}^\star) \neq \emptyset\} = O_P(N^{-1})$ if $D_{i,j} | E_{ij} = O_P(N^{-1})$ for all $1 \leq i < j \leq k$. Finally, by delta method it is enough if $\Delta_i | E_{ij} = O_P(N^{-1})$ and $\Delta_j | E_{i,j} = O_P(N^{-1})$ for all $1 \leq i < j \leq k$.

To this end realize that

$$P(\Delta_i > c|E_{ij}) = E[P(\Delta_i > c|U_{i,s_i+l_{ij,i}:n_i}, E_{ij})|E_{ij}], \tag{16}$$

where the expectation is taken with respect to the conditional distribution of $U_{i,s_i+l_{ij,i}:n_i}|E_{ij}$ and $l_{ij,i}$ was defined in Web Appendix 7. Due to independence between doses and the properties of uniform distribution we have the following. If $l_{ij,i} = 0$,

$$\Delta_i|U_{i,s_i+l_{ij,i}:n_i} = u, E_{ij} \stackrel{\mathcal{D}}{=} \text{logit}(u + V) - \text{logit}(u)$$

where $V \sim (1-u)\text{Beta}(n_i - s_i, 1)$. On the other hand if $l_{ij,i} = 1$,

$$\Delta_i|U_{i,s_i+l_{ij,i}:n_i} = u, E_{ij} \stackrel{\mathcal{D}}{=} \text{logit}(u) - \text{logit}(u - V)$$

where $V \sim u\text{Beta}(s_i, 1)$.

In any case, (16), delta method, assumptions on $s_i$ and $n_i$, and well known properties of Beta distribution imply that $\Delta_j|E_{i,j} = O_P(N^{-1})$, provided that the conditional distribution $\text{logit}\, U_{i,s_i+l_{ij,i}:n_i}|E_{ij} = O_P(1)$. However, the proof in the Web Appendix 7 implies $\text{logit}\, U_{i,s_i+l_{ij,i}:n_i}|E_{ij} \xrightarrow{P} \beta_0 + x_i\beta_1$, and the Theorem 2.