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RESEARCH ARTICLE

STRONG LIMITING BOUNDS FOR NUMBER OF SCREENING SUBJECTS IN A MULTI CENTRIC CLINICAL TRIAL

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A B S T R A C T

This paper finds a limiting region for the number of subjects required and hence number of failed in screening test in multi-centric clinical trials. This situation follows a properly normalized independent vector sequences comprising of moving maxima ($Y_{k\,(n)}$) for m (>1) multi centric set up in clinical trials, where $1 \le k\,(n) \le n$. Results are given for bi-centric and multi-centric situations, under certain conditions on k (n).

INTRODUCTION

Inclusion of subjects or patients in a clinical trial depends on the screening test. As a result, suppose the study requires n subjects, it is customary to allow the subjects (>n) for screening to achieve n. It is not possible for a doctor to screen all the subjects in one day itself. However, in each centre doctors fixed equal number of subjects to be included in each day, so that total number of subjects included is equal to n. Subjects will be included based on the screening test. Subjects are screened till the required subjects pass the screening test. If subjects pass the screening test, they are included else are rejected. Rejected subjects are the failures. Thus the number of failures in each day differs. The number of failures and hence the number of screening subjects to make it to the trial till the fixed number of inclusions is reached on the j^{th} day follows Negative Binomial Distribution (NBD). Observe that the maximum failures moves and hence screening subjects , by leaving first few days of information on number of failures and considering the last k(n) days of information does not affect too much. This is exactly the moving maxima, which is due to Rothmann and Russo (1991). As this scheme of finding number of failures for fixed number of inclusion of subjects on each day is adopted at each center , the moving maxima of number of screening subjects, that include failures and test passed subjects, on j^{th} day constitute vector sequence of independent components of i^{th} centre moving maxima. Thus to provide optimum resources at the centre to minimize the cost involved , doctors /company might be interested to know the strong limiting regions in which the moving maxima of number of failures or number of screening subjects of multi-centre lie. In view of this, the following set up is planned to get the strong limiting regions for vector sequences of independent copies of moving maxima for Negative Binomial Distribution (NBD). However, for ease of computation, results are proved for bi-centric case. The results are stated for multi-centric vector sequences. Below the set up is explained.

Let r be the number of subjects passes the screening tests i.e. the sample size required for the multi-centric trial. Let $\{X_n , n \ge 1\}$ be a sequence of number of screening subjects required to meet r and is an independent identically distributed random variables (i.i.d.r.v) with common probability mass function

$$P(X=k) = {}^{(k-1)} c_{(r-1)}\, a^r\, (1-a)^{k-r},\ k=r, r+1, \ldots, 0<a<1.$$

Define, moving maxima $Y^i_{k(n)} = \max(X_{n+1} , X_{n+2} , \ldots, X_{n+k(n)})$ where k(n) is a sequence of positive integers , $2 \le k(n) \le n$, for i^{th} multi-centre ,i=1,2,3,….

Hebbar and Vadiraja (1997) have used following conditions on general k (n) to find the strong limiting bounds for moving maxima in continuous case.

K (n) is non-decreasing (1.1)

$$\sup\,[k\,(n+1) - k\,(n)] \le \mu \text{ (finite)} \tag{2.1}$$

and

$$K\,(n) = [n/ (\log n)^{t(n)}] \text{ where } t(n) \to \infty \text{ as } n \to \infty \tag{3.1}$$

Throughout, δ_l's, l=1, 2,.. are sufficiently small positive constants. Now the results are stated below. Let $c_n(x) = xa_n+b_n$, where a_n=-loglogn/ log (1-a), bn = -logn/log (1-a) are the real sequences.

Theorem 1 The almost sure limit set of the vector sequence $\{Y1k_{(n)} - a_n)/ b_n,\ Y^2_{K\,(n)} - a_n)/ b_n\}$ n≥1, coincides with the region $S_1 = \{(x, y):\ r-p-1 \le x, y \le r,\ x + y \le 2r-p-1\}\ 0 \le p < \infty$.

Theorem 2 The almost sure limit set of the vector sequence $\{Y1k_{(n)} - a_n)/ b_n, Y^2_{k(n)} - a_n)/ b_n ,\ldots, Y^l_{k(n)} - a_n)/ b_n \}$ n≥1,l>0 coincides with the region $S_1=\{(x,y,\ldots,z)$: r-p-1≤x,y,...,z ≤ r , x + y+..+z ≤ mr-p-1} 0≤p<∞.

Remark Let $Y^*_{k(n)} = \max(X_{n-k(n)+1}, X_{n-k(n)+2}, \ldots, X_n)$ be the backward moving maxima and backward. Then the above results hold good.

Proofs

The proof of Theorem 1 is built up through the following lemmas.

Lemma 1.2

For every ϵ>0, we have

$$\text{Const. } (\log n)^{-(x+p-r+1+\epsilon/8)} \le k(n)\,[1-F(c_n(x))] \le \text{Const.}(\log n)^{-(x+p-r+1+\epsilon/6)} \quad (1.2)$$

Lemma 2.2

Let $S_1 = \{(x, y)$: r-p-1 ≤ x,y ≤ r , x+y ≤ 2r-p-1

For every Є>0,

$$P(Y^1_{k(li)} > c_{li}(x+\epsilon), Y^2_{K(li)} > c_{li}(y) \text{ i.o.})=0 \quad (2.2)$$

$$P(Y^1_{k(li)} > c_{li}(x), Y^2_{K(li)} > c_{li}(y+\epsilon) \text{ i.o.})=0 \quad (3.2)$$

and $$P(Y^1_{k(li)} > c_{li}(x), Y^2_{k(li)} > c_{li}(y) \text{ i.o.})=1 \quad (4.2)$$

Where $l_i= [\exp(i^\theta)]$ and $\theta^{-1}=(x+y+2p-2r+2+\epsilon)$

Proof (2.2) is achieved as follows.

$$P(Y^1_{k(li)} > c_{li}(x+\epsilon), Y^2_{k(li)} > c_{li}(y)) = P(Y^1_{k(li)} > c_{li}(x+\epsilon))\, P(Y^2_{k(li)} > c_{li}(y))$$
$$= \text{const.}k2(l_i)\,(1-F(c_{li}(x+\epsilon))).\,(1-F(c_{li}(y)))$$
$$\le \text{const.}(\log l_i)^{-(x+p-r+1+\epsilon+\epsilon/6)-(y+p-r+1+\epsilon/6)} \quad (5.2)$$

By (1.2) and for every ϵ>0. Note that for i large, we have

$$\Theta(x+y+2p-2r+2+\epsilon+\epsilon/6+\epsilon/6)= 1 + \delta_1 \quad (6.2)$$

Where $\delta_1 = [\theta\,\epsilon/3] > 0$.

In view of (6.2) and (5.2),

$\Sigma\, P(Y^1_{k(li)} > c_{li}(x+\epsilon), Y^2_{K(li)} > c_{li}(y) <\infty$

Through B-C lemma, (2.2) follows. The proof of (3.2) is similar. The proof of (4.2) is established as follows.

Similar to (5.2) and (6.2),

$$P(Y^1_{k(li)} > c_{li}(x), Y^2_{k(li)} > c_{li}(y)) = \text{const.}k^2(l_i)(1-F(c_{li}(x))).(1-F(c_{li}(y)))$$
$$\ge \text{const.}(\log l_i)^{-(x+p-r+1+\epsilon/8)-(y+p-r+1+\epsilon/8)}$$
$$= \text{const.}\, i^{-\theta(x+y+2p-2r+2+\epsilon/4)}$$
$$= \text{const.}\, i^{-(1-\delta 2)}$$

Where $\delta_2 = \theta 3\epsilon/4>0$ for every ϵ>0 and i large. To prove (4.2), it is sufficient to show $Y^i_{k(li)}$'s are independent for all i large, i =1, 2,.. Observe that,

$L_i - k(l_i) + 1 - l_{i+1} = l_i\,[1-k(l_i)/l_i + 1/l_i - l_{i-1}/l_i] \to\infty$ for large I and for θ >0 i.e x+y ≤2r-p-1

As $l_{i-1}/l_i \to 1$ $(k(l_{i-1}) * l_{i-1}/l_{i-1*}l_i) \to 0$, $1- l_{i-1}/l_i \sim h\, i^{(\theta-1)}$

Hence, whenever θ>1, i.e. (x+y+2p-2r+2)<1

R.H.S (12.2) is ~ l_i as i→∞. Further for $(1+p)^{-1}<\theta\le 1$, the expression inside the square bracket of (12.2) is ~ $hi^{(\theta-1)}$ as i→∞, since $i^{(1-\theta)} * k(l_i)/l_i \to 0$

Thus, for $\theta> (1+p)^{-1}$, i.e. for x+y<2r-p-1,

R.H.S (12.2) tends to ∞ as i→∞.

Thus, the events under consideration are independent, for all i large.

Lemma 3.2 For all x≥r, y≥r with x+y>2r-p-1 and for every Є>0,

$$P(Y^1_{k(n)} > c_n(x+\epsilon), Y^2_{K(n)} > c_n(y+\epsilon) \text{ i.o.})=0 \quad (7.2)$$

Proof $P(Y^1_{k(n)} > c_n(x+\epsilon), Y^2_{k(n)} > c_n(y+\epsilon)) = \text{const.}k^2(n)(1-F(c_n(x+\epsilon))).(1-F(c_n(y+\epsilon)))$

$$\le \text{const.}(\log n)^{-(x+p-r+1+\epsilon+\epsilon/6)-(y+p-r+1+\epsilon+\epsilon/6)}$$
$$= \text{const.}(\log n)^{-(x+y+2p-2r+2+7\epsilon/3)} \quad (8.2)$$

For every ϵ>0, x+y>2r-p-1 and for n large,

$$x+y+2p-2r+2+7\epsilon/3 > 1+\delta_3,\ \delta_3=1+p+7\epsilon/3>0,\ 0\le p<\infty. \quad (9.2)$$

An appeal to (9.2), (8.2) and B_C lemma, the lemma is proved.

Lemma 4.2 For every Є>0 and x_0 = r-p-1

$$P(Y^1_{k(n)} < (x_0-\epsilon)\, bn \text{ i.o.})=0 \quad (10.2)$$
$$P(Y^2_{K(n)} < (x_0-\epsilon)\, bn \text{ i.o.})=0 \quad (11.2)$$

Proof

(10.2) is established by showing the following and (11.2) follows on similar lines.

$$P(Y^1_{k(n)} > (x_0-\epsilon)\, bn \text{ i.o.})=1 \quad 11.2)$$
$$P(Y^1_{k(n)} \le (x_0-\epsilon)\, bn \text{ and } Y^1_{k(n+1)} > (x_0-\epsilon)b_{n+1} \text{ i.o.})=0 \quad (12.2)$$

Note that,

$$P(Y^1_{k(n)} > (x_0-\epsilon)b_n) = \text{Const. } k(n)(1-F((x_0-\epsilon)b_n))$$
$$\le \text{Const. }(\log n)^{-(x-\epsilon/8+p-r+1+\epsilon/6)} \quad (13.2)$$

For every ϵ >0, $x_0 - \epsilon/8+p-r+1+\epsilon/6 =\delta_4$, $0<\delta_4<1$.

An appeal to (13.2) and B_C lemma, (11.2) is established. (12.2) is shown as follows.

$$P(Y^1_{k(n)} \le (x_0-\epsilon)\, bn \text{ and } Y^1_{k(n+1)} > (x_0-\epsilon)\, bn_{+1})$$
$$\le P(Y^1_{k(n)} \le (x_0-\epsilon)b_n \text{ and } \max(X_{n-k(n+1)+2},\ldots, X_{n-k(n)}, X_{n+1}) > (x_0-\epsilon)b_n)$$
$$= P(Y^1_{k(n)} \le (x_0-\epsilon)b_n) \bullet P(\max(X_{n-k(n+1)+2},\ldots, X_{n-k(n)}, X_{n+1}) > (x_0-\epsilon)b_n)$$
$$\le \text{Const. } F^{k(n)}((x_0-\epsilon)b_n))\bullet\{k(n+1)-k(n)\}(1-F((x_0-\epsilon)b_n))$$
$$\le \mu \exp\{-k(n)(1-F((x_0-\epsilon)\, bn))\} \bullet \{1-F((x_0-\epsilon)\, bn)\} \quad (14.2)$$

Using (2.1). By (3.1), for every ϵ >0, n large and for some a>0, with $G_n= k(n)(1-F((x_0-\epsilon)b_n))$ $(\log n)^{a-\epsilon} <G_n < (\log n)^{a+\epsilon}$ (15.2)

Fix M>0, so that M (a-ϵ) >1+ δ_5, δ_5>0 for large n. By (15.2) and (1.2),

$$\text{RHS } (14.2) \le \mu \exp\{-((\log n)^{a-\epsilon}\}(n)^{-1} \le \mu\, n^{-1}(\log n)^{-(1+\delta 5)} \quad (16.2)$$

In view of (15.2) and (16.2), (12.2) is established. Hence the lemma 4.2.

Proof of Theorem 1 S is a required limit set by lemmas 3.2 and 4.2. It is concluded with the fact that the limit set is necessarily closed from the lemma 2.2. This completes the proof of theorem1.

References

Rothmann, M.D and R.P. Russo (1991). Strong limiting bounds for a sequence of moving maxima. Statist. Probab. Lett. 11, 403-410.

Hebbar, H.V and N. Vadiraja (1997). Limit points of sequences of moving maxima, Statist.Probab. Lett. 34,13-18.

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