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Exploration of Systematic Biases in Phase III Clinical Trials

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The study of systematic biases is a well documented technique for differential non-responses.[1] In clinical research, many features that make their response useful can be identified, including those relating to problem base, patient centeredness, value for money, transparency and information gain.[2] However, the underlying feature of bias is not satisfied and fully understood. Our objective is to explore extreme systematic biases in phase III clinical trials and provide summaries of our findings.

A. Introduction

In this report, the potential effect of selection bias in phase III of clinical trials is studied.[3] According to literature, the solution behind these biases is undetermined due to the complexity of layers within clinical trial phases (I-IV).[4] Due to experimentation and not just observation, clinical trials are therefore more involved. For this reason, we focus only on phase III in clinical trials as they appear to be the most promising in delivering data at T_1.

i. Statistical Model

We begin by creating a simple two category statistical model, "Symptoms" and "No-Symptoms," at T_1 and T_2 for phase III clinical trials.

Table 1. NUMBERS OF PATIENTS WITH SYMPTOMS AND NO SYMPTOMS

		Symptom status at time T_2	
		Symptoms	*No Symptoms*
Symptom status at time T_1	*Symptoms*	N_{ss}	N_{sn}
	No Symptoms	N_{ns}	N_{nn}

Using the notation of Table 1, the true symptoms rate at T_1, is given by

$$R_1 = (N_{ss} + N_{sn}) \,/\, N \qquad \textbf{Eq. 1}$$

and at T_2 by

$$R_2 = (N_{ss} + N_{ns}) \,/\, N \qquad \textbf{Eq. 2}$$

where

$$N = N_{ss} + N_{ns} + N_{sn} + N_{nn} \qquad \textbf{Eq. 3}$$

When the actual sampling for the selected trial phase begins, the classification of the data will not be accurate since not all patients designated for the research will take part in the study. Therefore, a more involved model is necessary. In Table 2, a simple three category statistical model, "*Symptoms*," "*No-Symptoms*," and "*Lost to Follow-up*" at T_1 and T_2 for phase III clinical trials, is introduced. After T_2 of a phase III trial, nine frequencies in this table will be known. We assume here that patients who do not take part in the study at either T_1 or T_2 can still be counted, so that the frequency F_{oo} is known.

Table 2. OBSERVED NUMBER OF PATIENTS IN VARIOUS CATEGORIES

		Symptom status at time T_2		
		Symptoms	*No Symptoms*	*Lost to Follow-up*
Symptom Status at time T_1	*Symptoms*	F_{ss}	F_{sn}	F_{so}
	No Symptoms	F_{ns}	F_{nn}	F_{no}
	Lost to Follow-up	F_{os}	F_{on}	F_{oo}

We state at this point that due to the complexity and privacy of much of the data collected from clinical trails, F_{oo} either remains unknown or a rough estimate of it may become available. However, its value does not effect the findings of the rest of the eight frequencies and subsequently, its respective estimations of the symptom rates.

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We construct an elementary expectation model and extend Table 2. Let:

P_n = Probability that a "No-Symptoms" person actually appears at T_1

P_s = Probability that a "Symptoms" person actually appears at T_1

P_{nn} = Probability that a drug was administered and an individual appeared at T_2 given that the drug was administered and that that he/she appeared at T_1 and showed "No-Symptoms" at both T_1 and T_2

P_{sn} = Probability that a drug was administered and an individual appeared at T_2 given that the drug was administered and that that he/she appeared at T_1 and showed "Symptoms" at T_1 and "No-Symptoms" at T_2

P_{ns} = Probability that a drug was administered and an individual appeared at T_2 given that the drug was administered and that he/she appeared at T_1 and showed "No-Symptoms" at T_1 and "Symptoms" at T_2

P_{ss} = Probability that a drug was administered and an individual appeared at T_2 given that the drug was administered and that that he/she appeared at T_1 and showed "Symptoms" at both T_1 and T_2

Finally, let Q_{ss}, Q_{sn}, Q_{ns}, and Q_{nn} represent probabilities similar to P_{ss}, P_{sn}, P_{ns}, and P_{nn} , except that *Q's* are conditional on the patient not showing symptoms at T_1. Ideally, each of these probabilities would equal its counterpart (ex. P_{ss}=Q_{ss})because all patients in the clinical trial are theoretically included in the sample. However, lost to follow-up problems will almost always ensure that *P's* and *Q's* are *not* always in unity. Therefore, exploration of expected sample numbers is an attractive option given three-by-three classification analysis. These expectations are displayed in Table 3.

Table 3. EXPECTED SAMPLE NUMBERS

		Symptom status at time T_2		
		Symptoms	*No Symptoms*	*Lost to Follow-up*
Symptom status at time T_1	*Symptoms*	$N_{ss}P_sP_{ss}$	$N_{sn}P_sP_{sn}$	$N_{ss}P_s(1-P_{ss}) + N_{sn}P_s(1-P_{sn})$
	No Symptoms	$N_{ns}P_nP_{ns}$	$N_{nn}P_nP_{nn}$	$N_{ns}P_n(1-P_{ns}) + N_{nn}P_n(1-P_{nn})$
	Lost to Follow-up	$N_{ss}(1-P_s)Q_{ss} + N_{ns}(1-P_n)Q_{ns}$	$N_{sn}(1-P_s)Q_{sn} + N_{nn}(1-P_n)Q_{nn}$	$N_{ss}(1-P_s)(1-Q_{ss}) + N_{sn}(1-P_s)(1-Q_{sn}) + N_{ns}(1-P_n)(1-Q_{ns}) + N_{nn}(1-P_n)(1-Q_{nn})$

ii.The Study of Identical patients

Table 2 can be used to construct an estimator based *only* on patients who are observed *both* at T_1 and T_2 . It can be seen that the number of patients who have symptoms at T_1 and are found to either be lost to follow-up or not at T_2 is given by $F_{nn} + F_{ns}$. Consequently, the number of patients who have no symptoms at T_1 and either have been lost to follow-up or not at T_2 is given by $F_{sn} + F_{ns}$. We can then state that the symptoms rate at T_1, based only on those patients who appear both at T_1 and T_2, is given by:

$$\hat{R}_1 = (F_{ss} + F_{sn})/ F \qquad \textbf{Eq. 4}$$

where

$$F = F_{ss} + F_{sn} + F_{ns} + F_{nn} \qquad \textbf{Eq. 5}$$

The symptom rate at T_2 for this same group of identical patients is given by:

$$\hat{R}_2 = (F_{ss} + F_{ns})/ F \qquad \textbf{Eq. 6}$$

where

$$F_{sn} = F_{ns} \qquad \textbf{Eq. 7}$$

Since we assume that we are exploring a large clinical trial, under the model of section 2, we neglect sampling variability and eq. 7 becomes

$$N_{sn}P_sP_{sn} = N_{ns}P_nP_{ns} \qquad \textbf{Eq. 8}$$

In this case there is no overall change in no-symptoms response and eq. 8 can be expressed as

$$P_s/P_n = P_{ns}/P_{sn} \qquad \textbf{Eq. 9}$$

The change in proportions of the observed symptom rate will occur even though there is no change in the true symptom rate. An easier way to interpret Eq.9 is by,

$$P_{1s}/P_{1n} = P_{2s}/P_{2n} \qquad \textbf{Eq. 10}$$

where the ratio of the probability of a patient attending a trial as demonstrating symptoms to the probability of a patient attending a trial as showing no-symptoms must be the same at T_1 and T_2 . Otherwise, there will be a change in the expected symptom rate from T_1 and T_2 .

In addition, we state, that due to the lack of information in determining the theoretical proposals of *P's* and *Q's* , we find difficulties in benchmarking our results and state summaries as is.

iii. Comparison of the estimates based on identical, unmatched(single), and all patients

The estimate based on "single" patients and the estimate based on all available patients can be formed by estimating $\hat{R}_{1t}$ and $\hat{R}_{2t}$. Their values are as such:

$\hat{R}_{1t}/1\text{-}\hat{R}_{1t} = (F_{ss} + F_{sn} + F_{so})/(F_{ns} + F_{nn} + F_{no}) \approx [(N_{ss} + N_{sn})/(N_{ns} + N_{nn})]^* (P_{1s}/(P_{1n})$ **Eq. 11**

and

$\hat{R}_{2t}/1\text{-}\hat{R}_{2t} = (F_{ss} + F_{sn} + F_{so})/(F_{ns} + F_{nn} + F_{no}) \approx [(N_{ss} + N_{ns})/(N_{ns} + N_{nn})]^* (P_{2s}/(P_{2n})$ **Eq. 12**

The estimates $\hat{R}_{1m}, \hat{R}_{2m}$ based on patients who appear only on a single occasion are given (in the simple case of independence) by,

$\hat{R}_{1m,}/1\text{-}\hat{R}_{1m} = (F_{sn})/(F_{ns}) \approx ([N_{ss}(1\text{-}P_{2s}) + N_{sn}(1\text{-}P_{2n})]/[N_{ns}(1\text{-}P_{2s}) + N_{nn}(1\text{-}P_{2n})])^* (P_{1s}/(P_{1n})$ **Eq. 13**

$\hat{R}_{2m,}/1\text{-}\hat{R}_{2m} = (F_{os})/(F_{on}) \approx ([N_{ss}(1\text{-}P_{1s}) + N_{ns}(1\text{-}P_{1n})]/[N_{sn}(1\text{-}P_{1s}) + N_{nn}(1\text{-}P_{1n})])^* (P_{2s}/(P_{2n})$ **Eq. 14**

According to Williams[1] $\hat{R}_1 - \hat{R}_2$, $\hat{R}_{1t} - \hat{R}_{2t}$, and $\hat{R}_{1m} - \hat{R}_{2m}$ do not have easy algebraic reductions and can be studied numerically. Below are comments about those results:

B. Experimental

In the following examples, we have constructed hypothetical clinical trials designed to emulate a study published in the *American Journal of Respiratory and Critical Care Medicine* entitled "Randomized Controlled Trial of Oral Antifungal Treatment For Severe Asthma.[5]" The purpose of this clinical trial was to study the effects of antifungal medication on patients with severe asthma. We've structured the following examples based on this phase III trial using randomized numbers and shifting the numbers and probabilities between examples, holding a constant sample size in effort to draw comparisons between each. In the preceding section, we will try to compare and comment on the results of this experiment as they may pertain to the effects that dropouts can have on clinical trials.

C. Results

Example A

First Stage Response Probabilities:

P_n =0.94 P_s =0.88

Second Stage Probabilities:

P_{nn} =0.97 P_{ns} =0.83 P_{sn} =0.95 P_{ss} =0.88
Q_{nn} =0.97 Q_{ns} =0.83 Q_{sn} =0.95 Q_{ss} =0.88

True Population Figures:

N_{nn} =710 N_{ns} =30 N_{sn} =30 N_{ss} =90

Table A1. EXPECTED SAMPLE NUMBERS

		Symptom status at time T_2			
		Symptoms	*No Symptoms*	*Lost to Follow-up*	*Total*
Symptom status at time T_1	*Symptoms*	*70*	*25*	*11*	*106*
	No Symptoms	*23*	*647*	*25*	*695*
	Lost to Follow-up	*11*	*45*	*3*	*59*
	Total	*104*	*717*	*39*	*860*

Table A2. Estimates of Symptom Rates (Percent)

R	*TRUE*	*Identicals*	*Total*	*Singles*
R_1	*14*	*11.05*	*15.18*	*38.74*
R_2	*14*	*10.81*	*14.17*	*23.83*
$R_1 - R_2$	*0*	*0.24*	*1.01*	*14.91*

Example B

First Stage Response Probabilities:

P_n =0.94 P_s =0.88

Second Stage Probabilities:

P_{nn} =0.95 P_{ns} =0.55 P_{sn} =0.95 P_{ss} =0.55
Q_{nn} =0.95 Q_{ns} =0.35 Q_{sn} =0.95 Q_{ss} =0.35

True Population Figures:

N_{nn} =710 N_{ns} =30 N_{sn} =30 N_{ss} =90

Table B1. EXPECTED SAMPLE NUMBERS

		Symptom status at time T_2			
		Symptoms	*No Symptoms*	*Lost to Follow-up*	*Total*
Symptom status at time T_1	*Symptoms*	*44*	*25*	*37*	*106*
	No Symptoms	*16*	*634*	*46*	*696*
	Lost to Follow-up	*4*	*44*	*11*	*59*
	Total	*64*	*703*	*94*	*861*

Table B2. Estimates of Symptom Rates (Percent)

R	*TRUE*	*Identicals*	*Total*	*Singles*
R_1	*14*	*8.01*	*15.18*	*80.24*
R_2	*14*	*6.97*	*9.39*	*15.79*
$R_1 - R_2$	*0*	*1.04*	*5.79*	*64.45*

Example C

First Stage Response Probabilities:

P_n =0.94 P_s =0.88

Second Stage Probabilities:

P_{nn} =0.97 P_{ns} =0.83 P_{sn} =0.95 P_{ss} =0.88

Q_{nn} =0.97 Q_{ns} =0.83 Q_{sn} =0.95 Q_{ss} =0.88

True Population Figures:

N_{nn} =350 N_{ns} =80 N_{sn} =80 N_{ss} =350

Table C1. EXPECTED SAMPLE NUMBERS

		Symptom status at time T_2			
		Symptoms	*No Symptoms*	*Lost to Follow-up*	*Total*
Symptom status at time T_1	*Symptoms*	*271*	*67*	*40*	*378*
	No Symptoms	*62*	*319*	*23*	*404*
	Lost to Follow-up	*41*	*29*	*7*	*77*
	Total	*374*	*415*	*70*	*859*

Table C2. Estimates of Symptom Rates (Percent)

R	*TRUE*	*Identicals*	*Total*	*Singles*
R_1	*50*	*39.35*	*93.62*	*191.15*
R_2	*50*	*38.77*	*87.37*	*133.62*
$R_1 - R_2$	*0*	*0.58*	*6.25*	*57.53*

As previously stated, in all of the above examples we have held our sample size constant and additionally, used identical first stage probabilities in each in effort to draw comparison. In both examples A and B we have kept our true population figures constant leaving us with a true, constant symptom rate of 14%. In example C, however, we raised our values to obtain a constant symptom rate of 50%, in order to explore what happens when our true symptom rate increases.

In example A, our total symptom rates at T_1 and T_2 are 15.18 and 14.17 respectively, which are both very close to our true symptom rates. The identical symptom rates are also fairly close to the true rates however, the singles rates are significantly larger than true. In this example, we've used identical P and Q values.

In example B, however, we have decreased our probabilities as well as varied the probabilities between P's and Q's. While both the identical and total rates are still fairly close to true, this has a drastic effect on the singles rates, causing them to skyrocket to more than 4 times the true rate.

Example C is the least representative example, but perhaps the most telling. Unlike Examples A and B, Example C represents a true population rate of 50%. The rates for identical are vastly underrepresented while the rates for total and singles grossly overrepresent the true symptom rates. Like Example A, Example C uses equal values for P's and Q's but represents an evidently biased estimate of symptom rates.

Conclusion

In this report, we have explored the systematic bias in phase III clinical trials. Although it is still unclear as to how to eliminate systematic bias in clinical trials due to dropouts, we can definitively state that this bias does in fact exist and some known factors contribute to its presence.

Estimating rates with a low true symptom rate results in seemingly unbiased estimated rates. However, as the true population of patients exhibiting symptoms increases, our estimates of symptom rates become increasingly more biased. While population figures appear to play a role in the presence of bias, conditional probabilities play a seemingly small role in the estimation of symptom rates in clinical trials.

References

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