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A Survival Analysis Instead of an Endpoint Analysis for Antibiotic Data

Karl E. Peace[1]

ABSTRACT

Phase II or Phase III clinical trials of new antibiotic compounds are usually positive controlled with two treatments: the new antibiotic compound versus an already marketed compound, and incorporate a randomized parallel design. Patients are on treatment for a specified period, are seen at various times during the period, and are seen at least once following the cessation of treatment. The efficacy variable is cure, microbiological and/or clinical. A clinical cure, for example, is typically defined as a complete abatement of signs and symptoms of the infection by the end of treatment and at the first post-treatment follow-up. Analyses of efficacy data are usually restricted to endpoint analyses of the proportions of patients cured. These analyses ignore the time of cure. Survival data or time-to-event analysis methods would, however, incorporate both the cure and the time at which it occurred. In a prospective sense, survival analyses of the efficacy data do not apply since it is not possible to classify a patient as cured or not cured during the treatment period. Retrospectively, however, a patient may be so classified and the "cure" located where it occurred. Survival analysis methods, the Mantel-Haenszel Procedure, for example, may then be applied treating time to cure as response, to test the hypothesis of no treatment difference. Withdrawals from the trial may also be incorporated in the analysis.

Key Words: Antibiotic Clinical Trials, Endpoint Analysis, Survival Analysis

I. INTRODUCTION

A prospective randomized clinical trial with a parallel design is conducted to compare two therapy regimens in the treatment of a chronic disease; for example, chronic urinary tract infections (UTIs). In such trials, after satisfying entry criteria, patients would be randomly assigned to the two treatment groups. Then patients in Group I would receive treatment A (say) for a fixed length of time, and patients in Group II would receive treatment B for the same length of time. Typically, both groups would be treated on an outpatient basis and would be instructed to return for follow-up at various times within the treatment period, at the end of the treatment period, and at various times post-treatment. A measure of the efficacy of each treatment is the proportion of patients "cured" of the infection in each treatment group. "Cures" would be microbiological and/or clinical.

The definition of either type of cure involves observations made during the treatment period and at the first post-treatment follow-up. That is, a patient is considered microbiologically cured if the infecting pathogen shows negative by the end of the treatment period and also at the first post-treatment follow-up. Similarly, a patient is considered clinically cured if a complete abatement of signs and symptoms (of the infection} is observed by the end of the treatment period and at the first post-treatment follow-up.

[1] Fellow of the American Statistical Association, Georgia Cancer Coalition Distinguished Cancer Scholar, Senior Research Scientist & Professor of Biostatistics, Founding Director, Karl E. Peace Center for Biostatistics, Jiann-Ping Hsu College of Public Health, Georgia Southern University, PO Box 8015, Statesboro, GA USA 30460. Email address: kepeace@georgiasouthern.edu, peacekarl@cs.com

In such trials, it is a common practice to perform separate univariate analyses on the microbiological and clinical cure/non-cure efficacy data using endpoint categorical data methodology; e.g., Fisher's exact test or Pearson's chi-square. For various reasons (patient withdrawal due to adverse reactions, losses to follow-up, etc.) efficacy data on only a subset of the patients originally enrolled in the trial may be included in the analyses. Additionally, such analyses do not reflect different types of "cure patterns" over the treatment period. For example, a patient who experienced a complete abatement of signs and symptoms within the treatment period, at the end of the treatment period and at the first post-treatment follow-up and a patient who experienced a complete abatement at the end of the treatment period and at the first post-treatment follow-up would contribute the same information (both would be cures) in the analysis of the clinical efficacy data. Survival type analyses of the efficacy data would, however, allow for the different types of cure patterns to be reflected. Additionally, losses to follow-up could be appropriately weighted, and thus contribute information for as long as they were known to be in the trial.

Since the definition of cure requires a post-treatment observation, prospectively it would not be possible to classify a patient as being cured during the treatment period. Hence, in applying survival analysis methodology to the efficacy data, cures would be retrospectively located. Then time to "cure" would be synonymous with time to "failure" in the usual survival analysis nomenclature.

Thus, the effectiveness of the two therapy regimens may be compared by first assessing baseline comparability, then using an appropriate method [e.g., actuarial of Berkson and Gage [1], Kaplan-Meier [2], or Cox [3]] to estimate non-cure probability curves, and then testing the hypothesis of no difference between the regimens by an appropriate method [for example, Cox proportional hazards model regressing on prognostic variables or Mantel-Haenszel ([4], [5], [6]) adjusting for prognostic variables].

II. NOTATION AND METHOD

Let S_I denote the "non-cure function" (survival function in the usual nomenclature) of the target population represented by those patients in Group I, and S_{II} denote the non-cure function of the target population represented by those patients in Group II. The efficacy comparison of the two regimens may be formalized as H_o: $S_I = S_{II}$ versus a suitable alternative hypothesis, H_a. The following notation is more amenable to the Kaplan-Meier [2] procedure and to the Mantel-Haenszel ([4], [5], [6]) procedure than to the actuarial method or method of Cox [3]. Prognostic (or concomitant) information available on patients at the time of randomization is not notated (references 3, 4, 5 and 6 may be seen for utilization of such information). Further, except in the discussion of the Mantel-Haenszel statistic, the particular treatment group does not index the notation.

2.1 No Withdrawals, or Withdrawals Unweighted

Let N_o denote the number of patients evaluated for efficacy (microbiological or clinical) at the first post-treatment follow-up (N_o would be the number at entry if there were no protocol violations and/or no withdrawals). Let t_o denote the time at which treatment began ($t_o = 0$). Let t_i, $i = 1, 2, ..., v$, denote the times at which cures are located (t_i could represent the scheduled times or actual times follow-up during the treatment period: the

choice depending upon the size of v, the spacing of the scheduled times, and patient follow-up compliance; t_v denotes the end of the treatment period). Let t_{v+1}denote the time (nominal) of the first scheduled post-treatment follow-up. Let C_i denote the number of cures at time t_i; nC_i, the number not cured at time t_i; N_i, the number not cured just prior to time t_i; q_i, the proportion cured at time t_i ($q_i = C_i/N_i$); $p_i = 1-q_i$. Then the estimate of the non-cure function or cumulative proportion non-cured at time t_i, $\hat{S}_i$ is the product of the P_j, over all $j \le i$; $\hat{S}_i = \prod_{j \le i} P_j$, and the cumulative proportion cured at time t_i is $F_i = 1 - S_i$.

For illustration, suppose that v = 3. The location of the cures may be facilitated by a map of possible patient activity such as that given in Figure 1.

Table 1 would then provide a summary of the proportions non-cured. Estimated non-cure probability curves could then be constructed from the information in Table 1.

Table 1. Typical table for summarizing estimated non-cure rates, when no withdrawals occur

t_i	N_i	C_i	nC_i	q_i	p_i	$\hat{S}_i$	$\hat{F}_i$
$t_o=0$	N_o	0	N_o	0	1	1	0
t_1	N_1	c_1	nc_1	c_1/N_1	$1-q_1$	p_1	$1-\hat{S}_1$
t_2	N_2	c_2	nc_2	c_2/N_2	$1-q_2$	p_1p_2	$1-\hat{S}_2$
t_3	N_3	c_3	nc_3	c_3/N_3	$1-q_3$	$p_1p_2p_3$	$1-\hat{S}_3$
t_4							

Table 2 provides a convenient summary of the computations necessary for the value of the Mantel-Haenszel (4, 5, 6) statistic.

Table 2. Typical table for summarizing computations necessary for the value of the Mantel-Haenszel Statistic

t_i	Group	C_i	nC_i	N_i	C_{1i}	$E(C_{1i})$	$V(C_{1i})$
t_o	I	0	N_{10}	N_{10}	0	0	0
	II	0	N_{20}	N_{20}			
t_1	I	c_{11}	nc_{11}	N_{11}	c_{11}	$E(C_{11})$	$V(C_{11})$
	II	c_{21}	nc_{21}	N_{21}			
t_2	I	c_{12}	nc_{12}	N_{12}	c_{12}	$E(C_{12})$	$V(C_{12})$
	II	c_{22}	nc_{22}	N_{12}			
t_3	I	c_{13}	nc_{13}	N_{13}	c_{13}	$E(C_{13})$	$V(C_{13})$
	II	c_{23}	nc_{23}	N_{23}			
t_4	I	0	nc_{13}		0	0	0
	II	0	nc_{23}				
		TOTAL			$\sum_{i=1}^{3} C_{1i}$	$\sum_{i=1}^{3} C_{1i}$	$\sum_{i=1}^{3} C_{1i}$

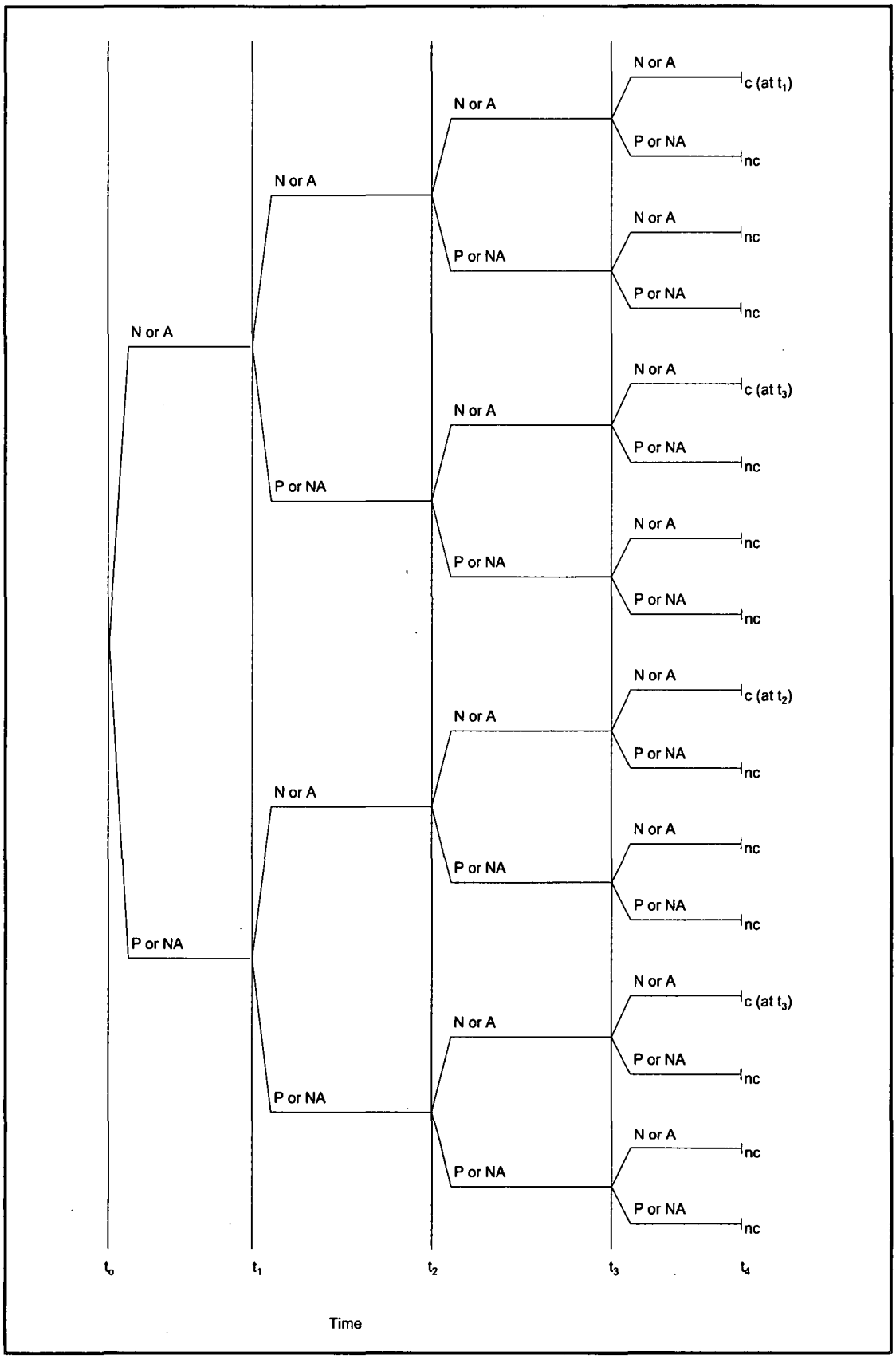

Figure 1. Map of possible patient activity for v=3; N denotes negative, P denotes positive, A denotes abated, and NA denotes not abated

The Mantel-Haenszel statistic, corrected for lack of continuity, may be written as,

$$\chi^2 = \frac{\left(\left|\sum_i c_{1i} - \sum((EC_{1i}))\right| - 1/2\right)^2}{\sum_i V(C_{1i})}, \qquad (1)$$

where the first subscript (one) references Group I, c_{1i} denotes the number of cures in Group I at time t_i, $E(C_{1i})$ denotes the expected value of C_{1i} at time t_i, and $V(C_{1i})$ denotes the variance of C_{1i} at time t_i. Both $E(C_{1i})$ and $V(C_{1i})$, are computed from 2 X 2 tables (Group I, Group II; cure, non-cure) constructed at each t_i utilizing the appropriate moment formulae for the hypergeometric distribution. Under the hypothesis H_o: $S_I = S_{II}$ χ^2 is distributed asymptotically as chi-square with 1 degree of freedom.

It is noted that the hypothesis above is equivalent to the hypothesis: H_o: $F_I = F_{II}$. Parenthetically the test based upon the Mantel-Haenszel Statistic could not be applied utilizing the cumulative numbers cured due to correlated observations. There is no problem in applying the test utilizing the numbers cured at a particular time obtained from the tables summarizing the non-cure rates. It may be noted that in such tables the number of cures, c_i, at a particular time, t_i, is removed from the number, N_i, possible to be cured at t_i before obtaining the number possible to be cured at time t_{i+1}.

2.2 Withdrawals due to Loss to Follow-Up Weighted

Let N_o denote the number of patients entering the study. Let t_i, C_i, c_i, nC_i, nc_i, q_i, p_i, $\hat{S}_i$ and $\hat{F}_i$ have the same identification as in section 2.1. Let W denote withdrawals, W_{fi} denote the number of withdrawals due to loss to follow-up just after time t_i, and W_{oi}, the number of withdrawals due to other causes just after time t_i, i = 0, 1, ..., v. Further, let $W_{fi} = \sum j W_{fij}$. Note that for i > 0, W_{fi} may consist of patients of at least two "types" - the maximum number of types being 2^i, and dependent on the observed response (negative or positive, abated or not abated) at time t_i. Let N_{i+1} denote the number possible to be cured at time t_{i+1}, i = 0, ..., v-1 ($N_{i+1} = N_i - C_i - W_{fi} - W_{oi}$). Let N(nc) denote the number observed non-cured at the first post-treatment follow-up: N(nc | n_1), denote the number observed non-cured at the first post-treatment follow-up of those observed negative (microbiological; abated, if clinical) at time t_1; N(|n_1), denote the number observed negative (abated) at time t_1; etc. Let P^*_{f1j}, denote the conditional proportion non-cured from the data when tracing the number evaluated for efficacy at the first post-treatment follow-up, from entry as though there were no withdrawals; e.g., $P^*_{fo1} = N(nc)/N_o$, $P^*_{f11}=(nc|n_1)/N(|n_1)$, etc. Let N'_{i+1} denote the effective number exposed to the "risk" of being cured $\left(N'_{i+1} = N_{i+1} + \sum jP^*_{fij} W_{fij}\right)$. Finally let q_i denote the proportion cured at time t_i given non-cured at time t_{i-1} $\left(q_i = c_i / N'_i\right)$.

Again for the purpose of illustration, suppose v=3. Figure 2 and Table 3 are the analogues of Figure 1 and Table 1.

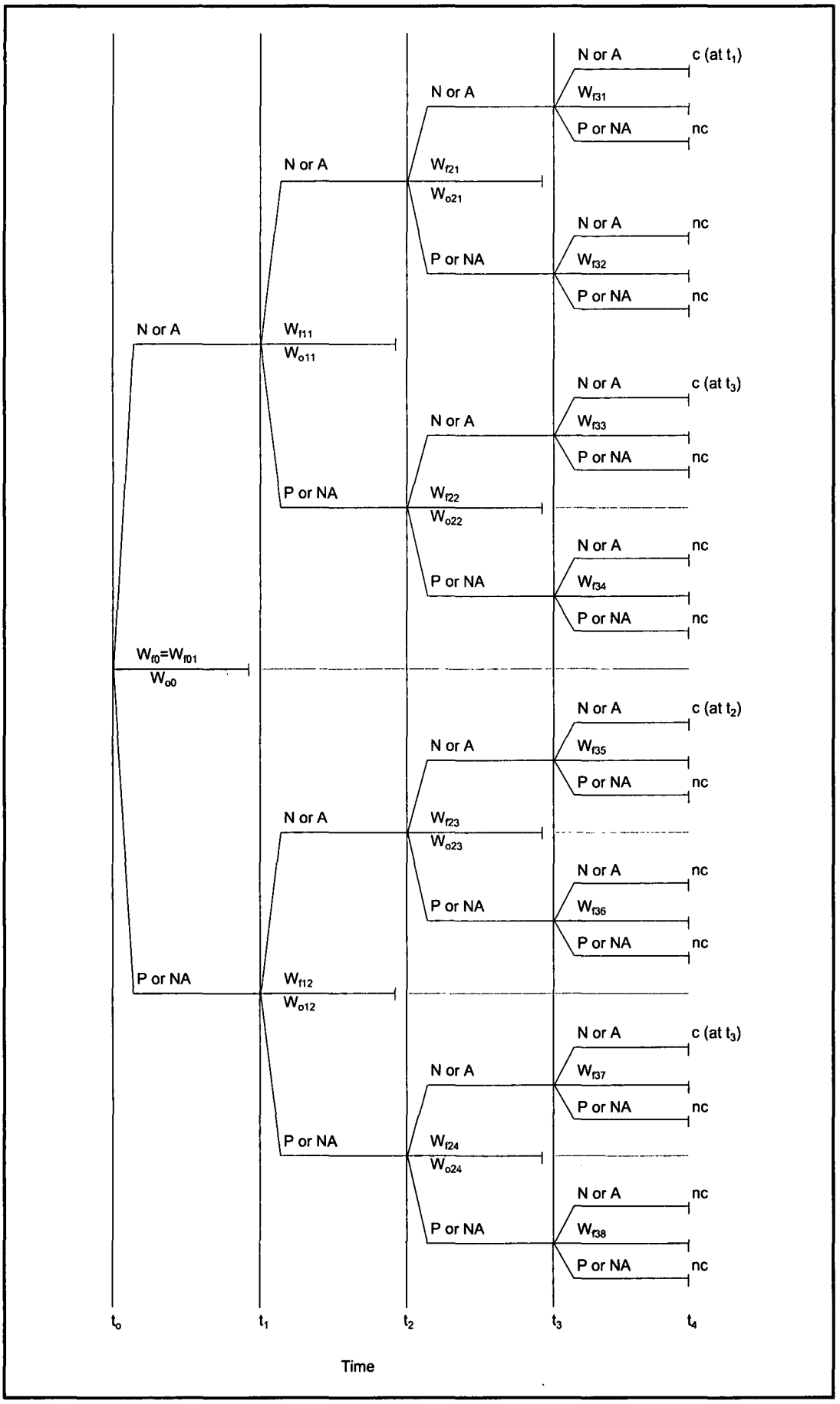

Figure 2. Map of possible patient activity for v=3 when withdrawals for loss to Follow-up are weighted. Notation in the table is explained in the text

Table 3. Typical table for summarizing estimated non-cure rates, when withdrawals due to loss to follow-up are weighted

t_i	N_i	W		C_i	nC_i	N_i	q_i	p_i[1]	$\hat{S}_i$[2]	$\hat{F}_i$[3]
		W_{fi}	W_{oi}							
t_o	N_o	0	0	0	N_o	N_o	0			
		W_{f0}	W_{o0}							
t_1	N_1			c_1	nc_1	N_1	c_1/N_1			
		W_{f1}	W_{o1}							
t_2	N_2			c_2	nc_2	N_2	c_2/N_2			
		W_{f2}	W_{o2}							
t_3	N_3			c_3	nc_3	N_3	c_3/N_3			
		W_{f3}	W_{o3}							
t_4										

[1] $p_i = 1 - q_i$; [2] $\hat{S}_i = \prod_{j \le i} p_j$;

[3] $\hat{F}_i = 1 - \hat{S}_i$

Note: Notation used in the table is explained prior to Figure 2.

A table for summarizing the computations necessary for the value of the Mantel-Haenszel statistic would be the same as Table 2 with N_i' replacing N_i.

III. AN EXAMPLE

As an example[2] suppose that a trial, as discussed in section 1 was conducted with a treatment period of ten days and that patients had follow-up on each day. Further suppose: (i) that 100 patients in each treatment group were evaluated for efficacy at the first post-treatment follow-up; (ii) that the groups of 100 each were comparable at baseline with respect to possible prognostic variables (e.g. sex, age, weight, height, race or ethnicity, number of previous UTI's, localization of present UTI, and signs and symptoms total) and their incidences of adverse experiences were low and roughly the same; (iii) that 90 cures (clinical, say) were among each of the 100 patients; and (iv) that the distribution of the cures across therapy days (and frequencies) from which patients experienced an abatement of signs and symptoms through the first post-treatment follow-up was:

Group I	1(40)	2(14)	3(14)	4(12)	5(4)	6(3)	7(3)	8(0)	9(0)	10(0)
Group II	1(0)	2(0)	3(3)	4(3)	5(4)	6(2)	7(4)	8(4)	9(20)	10(50)

[2]The data in this example are contrived. Real data have been analyzed by the author using the methods (including weighting withdrawals) described, but is not presented due to confidentiality.

No difference between the two treatments using the proportion cured in each treatment group as the response variable is observed. Consequently, no endpoint analysis would detect a treatment difference.

Estimating the "non-cure" probabilities as suggested in Table 1 and plotting gives the "non-cure" patterns in Figure 3. Certainly the "non-cure" patterns as reflected in Figure 3 suggest that treatment A is the superior treatment.

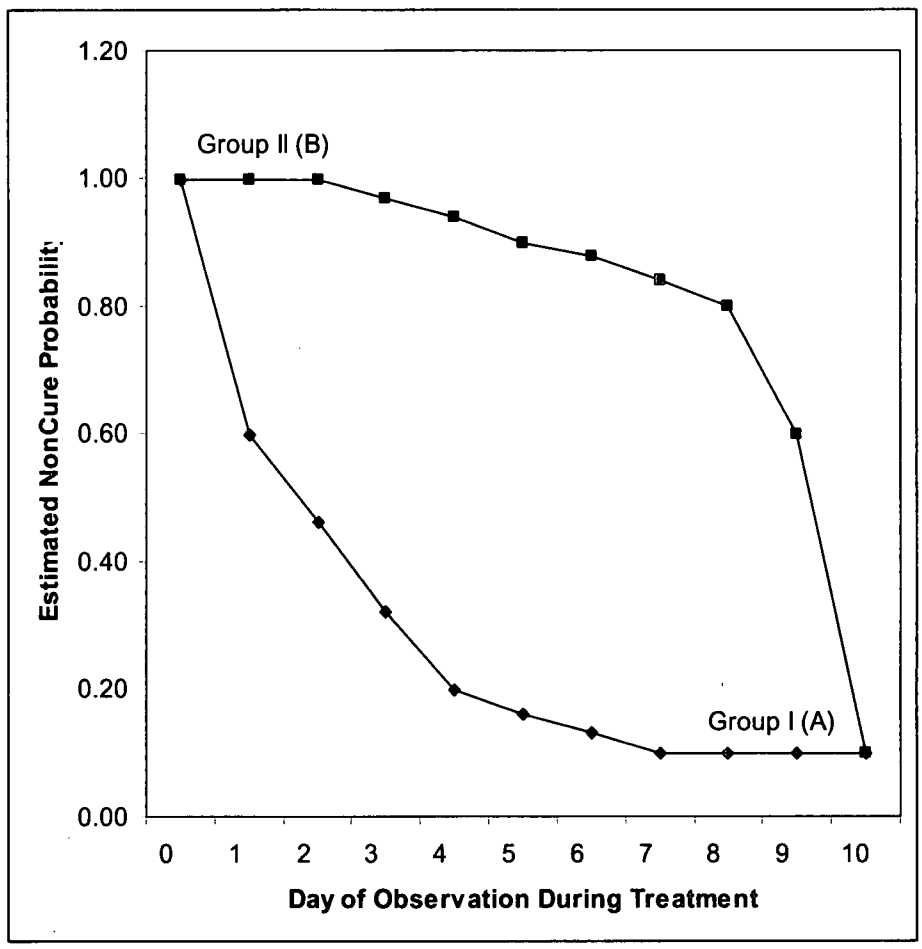

Figure 3. Estimated non-cure probability curves utilizing the data in the example of section three

The Mantel-Haenszel procedure strongly detects this difference with a χ^2 value of 78.11 (Table 4), which is highly statistically significant (P<0.0001).

Table 4. Summary of computations necessary for the value* of the Mantel-Haenszel statistic for the example data

t_i	Group	C_{ji}	nC_{ji}	N_{ji}	C_{1i}	$E(C_{1i})$	$V(C_{1i})$
	I	40	60	100			
1	II	0	100	100	40	20.00	8.04
	I&II	40	160	200			
	I	14	46	60			
2	II	0	100	100	14	5.25	3.01
	I&II	14	146	160			
	I	14	32	46			
3	II	3	97	100	14	5.36	3.26
	I&II	17	129	146			
	I	12	20	32			
4	II	3	94	97	12	3.72	2.49
	I&II	15	114	129			
	I	4	16	20			
5	II	4	90	94	4	1.40	1.09
	I&II	8	106	114			
	I	3	13	16			
6	II	2	88	90	3	0.75	0.62
	I&II	5	101	106			
	I	3	10	13			
7	II	4	84	88	3	0.90	0.74
	I&II	7	94	101			
	I	0	10	10			
8	II	4	80	84	0	0.43	0.37
	I&II	4	90	94			
	I	0	10	10			
9	II	20	60	80	0	2.22	1.55
	I&II	20	70	90			
	I	0	10	10			
10	II	50	10	60	0	7.14	1.77
	I&II	50	20	70			
		TOTAL			90	47.17	22.94

* - $\chi^2 = (90 - 47.17 - 0.5)^2 / 22.94 = 78.11$

Some modifications in the observed cure patterns would also lead to the endpoint analyses failing to detect a treatment difference and survival analyses detecting a difference; e.g., if at day 10 there were 41, 42 ..., 49 cures in Group B. These examples are similar to those (in the usual survival nomenclature) alluded to by Mantel [6].

IV. DISCUSSION

Data generated in a setting such as that described in sections 1 and 2 are commonly analyzed by endpoint contingency table methods. Analyses of the survival type have been suggested as alternative methods [7]. It is felt that such analyses utilize the data more fully than do endpoint ones. The reasons for this are: (i) such analyses reflect the "cure"/ "non-cure" patterns over the treatment period: and (ii) such analyses allow for withdrawals due to loss to follow-up to be incorporated.

Endpoint analyses may be applied more easily to test the hypothesis of no treatment difference than survival type analyses. There are however situations -- such as the example presented, which are design and/or data dependent in which a survival type analysis appears to be the analysis of choice. Even if one performs an endpoint analysis to test the hypothesis of no treatment difference, accompanying the result with graphs of the estimated non-cure curves is useful information in visualizing treatment differences in terms of earlier onset of cure.

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