Tipping Point Analyses: A Case Study

Emilea Norris[1], Graham Carron[1]
[1]Biostatistics Department, PPD, Wilmington, NC 28401

Abstract

The purpose behind a tipping point analysis (TPA) is to find the point ("tipping point") at which the objectives of an underlying analysis are no longer met. TPAs have gained popularity in recent years as a tool to assess sensitivity to assumptions about missing data without additional modeling for a variety of analysis types. However, little guidance exists regarding methodologies for implementing a TPA. Various methods exist for a TPA with an underlying time-to-event analysis through which incremental adjustments of the censored observations achieve the tipping point, such as observed time of the censored event (earliest, latest, or random). As a result of recent experience with regulators, this presentation will illustrate TPAs and associated output based on actual data with a time-to-event endpoint. The impact of conversion order will be evaluated, as will the distributions of the different censored observations. Visual outputs summarizing different implementation methods will be included, along with interpretations of the overall results and comparison of TPA performance against the performance of another well-established approach.

1. Introduction

The limited amount of literature available for TPAs has involved mostly applications with simulated data to deliver the goal of this method to the reader. These initial applications of TPAs focused mainly on missing data.

The implementation of a TPA is to apply incremental adjustments to account for "missing" or "censored" data. The idea is to convert information for a subject in a fashion that may eventually influence the underlying analysis results.

In this presentation, the focus is to look at incremental adjustments based on time where the underlying analysis is time-to-event. As noted below, time is a continuous factor and thus can be sorted from earliest to latest, or latest to earliest. The possible number of approaches increases with more treatments. (Please see the discussion section found at the end for information on other TPAs based on different underlying analyses.)

Notes on Incremental Adjustments for Traditional Time-to-event TPA

- Time-to-event: Conversion order into TPA uses observed time of censored event

1-Treatment	
Approach 1	Earliest to Latest
Approach 2	Latest to Earliest

2-Treatments	Treatment A	Treatment B
Approach 1	Earliest to Latest	Earliest to Latest
Approach 2	Earliest to Latest	Latest to Earliest
Approach 3	Latest to Earliest	Earliest to Latest
Approach 4	Latest to Latest	Latest to Latest

- Complete Cross-product Pairing:
  The number of stages will be the cross-product of the number of censored observations **per** treatment group. (Number censored in Treatment A x Number censored in Treatment B.) Please see Appendix B for an example.

1.1 Modified Entry as Discussed with FDA: Simple Pairing Entry

The number of stages in a traditional TPA are inflated, thus in the TPA provided to the FDA a modification was used. A simple pairing entry was used instead of the cross-product paring. Key points:

- Essentially, this is a subset of the traditional TPA's cross-product entry. A "pair" of subjects enters the stage (one subject from each treatment). The number of stages will be the maximum number of censored observations in **either** treatment group.
- Observed time of censored event is still used for entry order.

1.2 Experimental TPA Approaches

These approaches were explored for this presentation. A random increment was based on the idea that "true" data is never orderly since natural occurrences are random. List entry was considered as a way to see if one treatment influenced the results up through a certain time point.

Experimental: Random-Random Increments, with Simple Pairing Entry

- Each censored observation is given a random number. [used SAS v9.2 Rand('Exponential') function]
- The pair of subjects enters the stage based on their random number.

Experimental: List Entry

- Only 1 subject enters the stage, based on their censored time, irrespective of treatment group.

2. Our Data

This presentation uses actual analyses with actual data. Below are some summaries of this data.

1 year visit window Days 337-393	**INV**	**PLB**
Number of subjects	125	60
Number of subjects experiencing the event within 1 year	32	30
Number of subjects censored and without experiencing the event within 1 year*	14	15

INV=investigational product, PLB=placebo

*Subjects were censored due to death unrelated to the indication.

The events and censored observations had the following distributions:

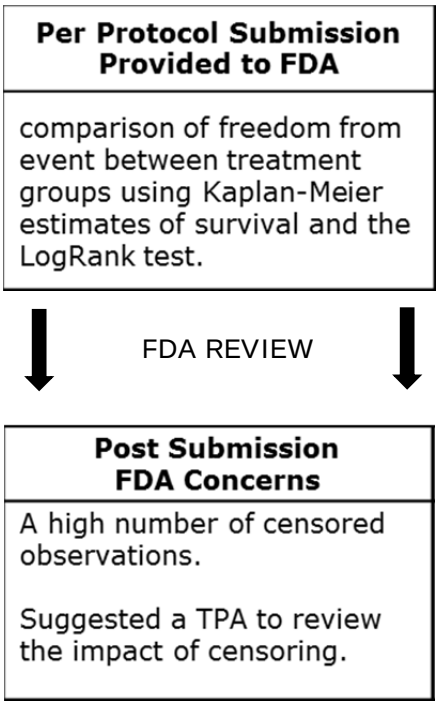
Distribution of Events	INV	PLB
0 to 30	26	29
>30 to 60	-	-
>60 to 90	2	1
>90 to 120	-	-
>120 to 150	2	-
>150 to 180	1	-
>180 to 337	1	-

Distribution of Censored Time	INV	PLB
0 to 30	4	8
>30 to 60	-	3
>60 to 90	-	1
>90 to 120	2	-
>120 to 150	1	1
>150 to 180	2	1
>180 to 337	5	1

Distribution of Events plus Censored Observations	INV	PLB
0 to 30	30	37
>30 to 60	-	3
>60 to 90	2	2
>90 to 120	2	-
>120 to 150	3	1
>150 to 180	3	1
>180 to 337	6	1

3. Procedure and Results

3.1 TPA per FDA



Key Notes from FDA Requests

o Each increment of the TPA is labeled as a "Stage".
o Stage 0 is the observed results
o Cut off for TPA requested as start of visit window for the 1 year visit
o Identify the subjects who enter the stage
o Submit SAS v9.2 PROC LIFETEST output
  o Observed,
  o Stage prior to tipping point,
  o Stage of tipping point,
  o and Stage after tipping point
  o Use of the "Simple Pairing Entry"
o Entry order was discussed with FDA, and it was decided that all 4 entry approaches should be explored.

TPA Results	Interpretations
All LogRank p-values were **significant**. No tipping point occurred (See Appendix A for displays)	Robust data: Changes in the probabilities over stages increased as expected. However, clear separation in favor of the INV. Ordering approaches had similar results.

3.2 Other Approaches

The performance of the 4 types of TPAs was compared, along with using the well-established multiple imputation method. The LogRank p-value was the main comparison factor.

Complete TPA

Possible Stages: Treatment INV 1 to 14, Treatment PLB 1 to 15
Maximum number of combinations: 14 x 15 = 210
(See Appendix B for information on displays.)

Application of List TPA

Highest number of Events and Censored observations occurred at 0 to 30 days. As noted in Section 2, there were 4 INV subjects and 8 PLB subjects that were censored in the observed analysis. Thus, applying this listing order approach, Stage 12 of a List TPA would result in all 12 censored subjects up through 30 days enter the analysis.

At stage 12, the event probabilities per treatment are INV 0.289, PLB 0.636.

Comparison: Multiple Imputations

- Steps taken
  - Data manipulation: censored observation values set to missing.
  - SAS v9.2 PROC MI was used to create 10 imputed datasets.
  - Each dataset run using the PROC LIFETEST.
- Mean study days to event
  - actual data: 237
  - after MI: 238
- Probability Estimates (Upper Limit of 97.5% One-Sided CI)
  - INV: ranged from 0.264 (0.351) to 0.320 (0.410)
  - PLB: ranged from 0.617 (0.738) to 0.717 (0.824)

Summary of Analyses with Actual Data

	LogRank p-value:	
Analysis	**Lowest**	**Highest**
Simple TPA	<0.0001	0.0002
Complete TPA	<0.0001	0.0050
Random TPA	<0.0001	0.0050
List TPA	<0.0001	0.0012
Multiple Imputation	<0.0001	<0.0001

4. Conclusions

Summary of TPA Results

Actual Results: No tipping point!!

The simple pairing TPA was performed using the 4 conversion order approaches. All censored observations up through the Study Day 337 was entered into the TPA. The LogRank test was used to indicate the separation or similarity of the two treatments. In the Simple TPA reviewed by the FDA and presented here, no tipping point was observed as all LogRank p-values were significant and probability estimates were in favor of the investigational product (INV). This shows the robustness of the analysis to assumptions about censored data.

Comparisons to Other TPA Approaches

All results were found to be similar after performing the other approaches with our data.

Complete TPA: Visual plots are best when using this approach, however, a tabular format can also be used. We suggest to first review how many stages will be required.

Random TPA: In this approach, we replaced the traditional incremental order (ex. Earliest to Latest) with a random order. An advantage shows that this aligns with unpredictability of events as seen in practice.

List TPA: The traditional incremental ordering (ex. Earliest to Latest) was applied without consideration to treatment group. When using this approach, special attention needs to be made to when censoring is occurring. If a high number of censoring occurs early for one treatment, then a tipping point could be seen earlier on. Our data witnessed the higher number of censoring for Placebo prior to day 30, however this would only show more separation between the treatments and in favor to the Investigational treatment.

Pairing vs single entry approaches

These two items become important when more than one treatment is included in a TPA. If a pair of subjects enter a stage, this is being fair to both treatments, in the sense that each treatment has the option to be incrementally adjusted at the same stage. If single order is used, like List TPA, a tipping point maybe seen early if data for one treatment causes significantly more increments for that treatment versus the other treatment(s).

5. Further Information and Discussions

When initially planning a TPA, there are some considerations to think about. These can help save you time!

- Constraints for underlying analysis?
- What is the most conservative scenario?
- Clinical meaning?

When to do a TPA	What has been seen	Possibilities
	o Ad hoc requests by regulatory authority mostly seen. o Planning purpose. TPA can be setup on assumptions before data is collected.	o Could this be used in place of sensitivity analyses for falsified data?

Further Applications of TPA	Data concerns	Analyses methods
	o Missing data o Censored data o Errors in completed data	o Binomial o Time to event o Any underlying analysis

Acknowledgements

We would like to give special thanks to Kevin Lawson (Senior Director, Biostatistics, PPD) and Andrew Hartley (Associate Statistical Science Director, Biostatistics, PPD). Both of them generously gave their guidance and support through the analyses and review of this topic.

Appendix A: Display for TPA table provided to FDA

Simple TPA (Earliest Censored Time) Kaplan-Meier Analysis

Stage	Treat-ment	Subject with Newly Added Event: Subject Imputed	Subject with Newly Added Event: Study Day	Number of Subjects: Event	Number of Subjects: Censored	Event Probability at 1 Year	Upper Limit of 97.5% One-Sided CI	Log-Rank p-value
0	**INV**	**N/A**	**N/A**	**32**	**93**	**0.262**	**0.350**	**<0.001**
0	**PLB**	**N/A**	**N/A**	**30**	**30**	**0.515**	**0.650**	
1	INV	A-1	0	33	92	0.269	0.357	<0.001
1	PLB	B-1	7	31	29	0.529	0.663	
2	INV	A-2	0	34	91	0.275	0.363	<0.001
2	PLB	B-2	8	32	28	0.543	0.675	
3	INV	A-3	0	35	90	0.282	0.370	<0.001
3	PLB	B-3	9	33	27	0.558	0.688	
4	INV	A-4	3	36	89	0.289	0.378	<0.001
4	PLB	B-4	14	34	26	0.573	0.701	
5	INV	A-5	94	37	88	0.297	0.385	<0.001
5	PLB	B-5	23	35	25	0.588	0.714	
6	INV	A-6	119	38	87	0.304	0.393	<0.001
6	PLB	B-6	26	36	24	0.604	0.728	
7	INV	A-7	145	39	86	0.312	0.402	<0.001
7	PLB	B-7	27	37	23	0.620	0.742	
8	INV	A-8	159	40	85	0.320	0.410	<0.001
8	PLB	B-8	27	38	22	0.636	0.756	
9	INV	A-9	163	41	84	0.328	0.418	<0.001
9	PLB	B-9	34	39	21	0.652	0.769	
10	INV	A-10	196	42	83	0.336	0.426	<0.001
10	PLB	B-10	36	40	20	0.668	0.783	
11	INV	A-11	249	43	82	0.344	0.434	<0.001
11	PLB	B-11	37	41	19	0.683	0.796	
12	INV	A-12	305	44	81	0.352	0.443	<0.001
12	PLB	B-12	74	42	18	0.700	0.810	
13	INV	A-13	323	45	80	0.360	0.451	<0.001
13	PLB	B-13	124	43	17	0.717	0.824	
14	INV	A-14	337	46	79	0.368	0.459	<0.001
14	PLB	B-14	162	44	16	0.733	0.837	
15	INV			46	79	0.368	0.459	<0.001
15	PLB	B-15	324	45	15	0.750	0.851	

Stage 0 observed results

Last stage start of window

Identify subject

Identify measure

Appendix B: Display options for a traditional TPA

Possible Stages: Treatment INV 1 to 14, Treatment PLB 1 to 15
Maximum number of combinations: 14 x 15 = 210

Table Example for Complete TPAs and Ordering, Kaplan-Meier Analysis				
			Subject with Newly Added Event	
Stage	**Sub-Stage**	TRT	Subject Imputed	Study Day
Starting Stage 0 as before…..				
0	**0**	INV	N/A	N/A
0	**0**	PLB	N/A	N/A
The ordering of the table depends on approach….				
1	**0**	INV	……	N/A
1	**1**	PLB	……	7
2	**0**	INV	……	N/A
2	**2**	PLB	……	8
3	**0**	INV	……	N/A
3	**3**	PLB	……	9
4	**0**	INV	……	N/A
4	**4**	PLB	……	14
Then continue table until combinations exhausted.