Practical Approach to Missing Item Imputation in Asthma Quality of Life Questionnaire

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Abstract

Patient reported outcomes are increasingly used in health research, including randomized controlled trials and observational studies. With these data we often compute scores that measure underlying scales – such as mental or social well-being. In this paper, practical imputation techniques to achieve appropriate calculations when there are missing items in questionnaires are applied to questionnaire data from two randomized clinical trials.

Key Words: Missing data, quality of life, asthma

1. Introduction

There has been increasing use of quality-of-life (QoL) instruments (i.e. patient reported outcomes) in drug development. For example, a widely used quality of life assessment in asthma is the Asthma Quality of Life Questionnaire (AQLQ) that includes both physical and emotional impacts of disease. The AQLQ has a total of 32 items in 4 domains/categories utilizing a 2-week recall. The categories include: Symptoms (11 items), Activity Limitation (12 items, 5 of which are individualized), Emotional Function (5 items), and Environmental Exposure (4 items). The items are scaled using a 7-point scale (7 = not impaired at all - 1 = severely impaired), with higher scores indicating a better quality of life. The Minimally Important Difference (MID) in score is 0.5 for overall quality of life and for each of the individual domains.

Missing items are more likely to occur with QoL data than with other clinical trial data, as most QoL instruments are self-administrated rather than being recorded by an external observer and patients may refuse to answer all or some of the items. The probability of missingness is likely to be associated with a patient's current state of health, particularly adverse drug reactions. Two kinds of approaches have been used to deal with this problem. One approach takes missing data in the domain and total scores into account in the analysis. Another approach is to impute missing values in the answer to each question before calculating the domain scores. Statistical analysis procedures then can be used for the imputed values.
The aim of this paper is to address the issue of missing item data in QoL by imputing item scores using easily applicable methods available and compare the approaches using the two asthma trials.

1.1 Regulatory Guidance

Health authorities have issued guidance on dealing with missing values in general clinical data and specifically for QoL data. Guidance was on the imputation of dropout data. The draft guidance by the FDA for patient-reported outcomes contains a subsection specifically for missing items. The guidance recommends specification of imputation methods in the analysis plan, though no recommendation for specific imputation approaches was given.

1.2 Missing Items in QoL Data

Data presented here are from three trials that used questionnaires to evaluate QoL for drugs used to treat severe to persistent asthma. Below Table 1 represents the frequencies of missing items in the questionnaires for these trials.

Table 1: Frequencies of missing items

Number of Missing items	n (%)
Trial 1	
0	3422 (99.65)
1	8 (0.24)
2	2 (0.06)
6	1 (0.03)
11	1 (0.03)
12	2 (0.06)
Trial 2	
0	3422 (99.65)
1	11 (0.32)
2	1 (0.03)
Trial 3	
0	2593 (93.27)
1	143 (5.14)
2	22 (0.79)
4	1 (0.04)
6	1 (0.04)
7	8 (0.29)
8	3 (0.11)
10	1 (0.04)
11	1 (0.04)
14	1 (0.04)
18	2 (0.07)
19	1 (0.04)
26	1 (0.04)
32	2 (0.07)

It is unusual to observe more than one item to be missing from a questionnaire for a given subject. From all three trials, all questionnaires were either complete or only a few items were missing.

Published work on dealing with missing items for QoL instruments is rare.
Some interesting facts regarding missing items are:

- Percentage of missing items is often small (0.5–1%).
- It varies considerably among trials as seen above.
- It varies based on duration of the trial.
- Probability of missing depends on patient's demographic characters such as age and gender.
- Missing items tend to cluster in a small number of patients and/or particular items.

2. Comparison of Imputation Methods Using Asthma Trial

Presented here are the results of analyses based on all available data and based on imputed data using the following imputation procedures: Last Observation Carried Forward (LOCF), longitudinal average, two way imputation (TWI) and corrected item mean imputation (CIMS) without truncation. Table 2 provides Least Square Mean of the imputed values for each domain in Trial 1 and Trial 2.

2.1 All Available Data, Last Observation Carried Forward (LOCF), Longitudinal Average

Table2: Change from Baseline Analysis of AQLQ

	Trial 1			
	Treatment1	Treatment2	Treatment1[d]	Treatment2[d]
Total Score				
All Data[a]	0.44	0.06	0.44	0.08
Endpoint[b]	*0.41*	*-0.21*	*0.42*	*-0.17*
Average[c]	0.37	-0.05	0.38	-0.04
Symptoms Domain				
All Data[a]	0.49	0.04		
Endpoint[b]	0.49	-0.28		
Average[c]	0.45	-0.08		
Activity Limitation Domain				
All Data[a]	0.35	0.03		
Endpoint[b]	0.29	-0.19		
Average[c]	0.28	-0.02		
Emotional Function Domain				
All Data[a]	0.42	0.03		
Endpoint[b]	0.44	-0.27		

Average[c]	0.39	-0.08		
Environmental Stimuli Domain				
All Data[a]	0.51	0.23		
Endpoint[b]	0.46	0.06		
Average[c]	0.39	0.07		
Trial 2				
	Treatment1	Treatment2	Treatment1[d]	Treatment2[d]
Total Score				
All Data[a]	0.61	0.36	0.64	0.34
Endpoint[b]	0.49	-0.01	0.52	-0.08
Average[c]	0.48	0.07	0.51	0.04
Symptoms Domain				
All Data[a]	0.64	0.34		
Endpoint[b]	0.52	-0.08		
Average[c]	0.51	0.04		
Activity Limitation Domain				
All Data[a]	0.55	0.35		
Endpoint[b]	0.41	0.02		
Average[c]	0.42	0.06		
Emotional Function Domain				
All Data[a]	0.63	0.39		
Endpoint[b]	0.52	0.02		
Average[c]	0.50	0.12		
Environmental Stimuli Domain				
All Data[a]	0.72	0.45		
Endpoint[b]	0.59	0.16		
Average[c]	0.50	0.15		

a: all available data
b: last post-baseline non missing AQLQ item carried forward
c: longitudinal average
d: Only those with at least two-thirds non-missing responses in each of the four domains of AQLQ to form the total score

2.1.1 Two Way Imputation (TWI)

This method imputes item j of subject i by

PMi + IMj – OM

Where PM_i is the subject mean of his or her observed item scores, IM_j is the mean of item j over all subjects and OM is the overall mean across all subjects and items.

Below Table 3 illustrates the use of TWI imputation using two trial data provided above.

Table 3: TWI Imputation

Trial 1				
	Treatment1	Treatment2	Treatment1[d]	Treatment2[d]
Total Score				
All Data[a]	0.44	0.06	0.45	0.08
Endpoint[b]	0.41	-0.21		
Average[c]	0.37	-0.05	0.38	-0.04
Trial 2				
	Treatment1	Treatment2	Treatment1[d]	Treatment2[d]
Total Score				
All Data[a]	0.61	0.36	0.63	0.38
Endpoint[b]	0.49	-0.01		
Average[c]	0.48	0.07	0.48	0.09

a: all available data
b: last post-baseline non missing AQLQ item carried forward
c: longitudinal average
d: impute by TWI

2.1.2 Corrected Item Mean Substitution (CIMS)

This imputation takes subject ability into account. It imputes item j of subject i by:

$PM_i(ind) / PM_i(all) \times IM_i$

Where $PM_i(ind)$ is the subject mean over all items observed from subject i; PMi(all) is the population mean of all items not missing from subject i; and IMj is the item mean over all available subjects.

One drawback common to both methods is that the imputed value might be out of the correct range of response. The general recommendation is to truncate the values at the ends of correct range. The model based approaches such as item response theory and Rasch Model which is not discussed here will handle this problem of out of range scores.

Table 4 illustrates the use of CIMS imputation using the trial data provided above.

Table 4 : CIMS Imputation

Trial 1				
	Treatment1	Treatment2	Treatment1[d]	Treatment2[d]
Total Score				
All Data[a]	0.44	0.06	0.45	0.08
Endpoint[b]	0.41	-0.21		
Average[c]	0.37	-0.05	0.38	-0.04

a: all available data
b: last post-baseline non missing AQLQ item carried forward
c: longitudinal average

d: impute by CIMS

Trial 2				
	Treatment1	Treatment2	Treatment1[d]	Treatment2[d]
Total Score				
All Data[a]	0.61	0.36	0.62	0.38
Endpoint[b]	0.49	-0.01		
Average[c]	0.48	0.07	0.49	0.06

a: all available data
b: last post-baseline non missing AQLQ item carried forward
c: longitudinal average
d: impute by CIMS

2.1.3 Impute by Adjusting Computed Score

Let *m = number of missing values* and *n = number of non-missing values*:

$$SCORE = (x_1 + x_2 + \cdots + x_n) + (m)\frac{(x_1+x_2+\cdots+x_n)}{n}.$$

This (above) is the mean substitution method and equates to

$$SCORE = \frac{n(x_1+x_2+\cdots+x_n)}{n} + (m)\frac{(x_1+x_2+\cdots+x_n)}{n}.$$

Calculating the mean value and imputing the mean value that is impute by mean substitution is equivalent to adding up the non-missing values and multiplying with a constant factor as above.

Table 5: Impute by Adjusting Computed Score

Trial 1				
	Treatment1	Treatment2	Treatment1[d]	Treatment2[d]
Total Score				
All Data[a]	0.44	0.06	0.43	0.06
Endpoint[b]	0.41	-0.21		
Average[c]	0.37	-0.05	0.37	-0.05

a: all available data
b: last post-baseline non missing AQLQ item carried forward
c: longitudinal average
d: impute by adjusting computed score=impute by mean

	Trial 2			
	Treatment1	Treatment2	Treatment1[d]	Treatment2[d]
Total Score				
All Data[a]	0.61	0.36	0.61	0.36
Endpoint[b]	0.49	-0.01		
Average[c]	0.48	0.07	0.48	0.07

a: all available data
b: last post-baseline non missing AQLQ item carried forward
c: longitudinal average
d: impute by adjusting computed score=impute by mean

Due to few missing data observed in these trials the imputation did not correct any of the estimates and all results were consistently identical, except in Trial1 where the imputed total score estimates were slightly lower in magnitude.

3. Conclusion

Missing item approaches were compared using AQLQ data from two asthma trials. Some general recommendations can be made based on these comparisons. For missing items in large domains such as symptom and ability domains in AQLQ, within domain imputations are recommended. It is also recommended to truncate the imputed values to avoid outliers that are outside the range of scores. All the approaches seem to have performed well for the specific data being studied. This paper concentrates on item level AQLQ imputation. If the imputed items will be used for the calculation of the scores, it is recommended consulting the instrument authors during the development of an imputation method. Missing whole questionnaire is not the topic of item imputation. It is also recommended that appropriate methods for item imputation be incorporated in a Statistical Analysis Plan (SAP) prior to submission to Health Authorities. In addition careful planning during the design stage will also avoid some of the missing data we are facing in our analysis.

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