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Missing Data Frequency and Correlates in Two Randomized Surgical Trials for Urinary Incontinence in Women

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Abstract

Introduction and Hypthosis—Missing data is frequently observed in clinical trials; high rates of missingness may jeopardize trial outcome validity.

Purpose—Describe rates of missing data over time, by type of data collected and to compare demographic and clinical factors associated with missingness among women who participated in two large randomized clinical trials of surgery for stress urinary incontinence, the Stress Incontinence Surgical Treatment Efficacy Trial (SISTEr) and the Trial of Midurethral Sling (TOMUS).

Methods—Proportions of participants that completed/missing each follow-up visit were calculated. Chi-square tests, Fisher's exact tests and t tests were used to compare women with and without missing data, as well as the proportion of completeness for each component of the composite primary outcome.

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Results—Data completeness for the primary outcome computation differed by trial, nearly double in TOMUS (62.3%) compared to SISTEr (35.7%). The rates of completed follow-up in-person visits decreased over time. A higher proportion of subjects attended all follow-up visits in the TOMUS trial and, overall, there was less missing data within the period that included collection of the primary outcome at 12 months. The highest proportion of completeness for the composite outcome variables was for the symptoms questionnaire (SISTEr: 100%, TOMUS: 99.8%) and the urinary stress test (SISTEr: 96.1%, TOMUS: 96.7%). In both studies, the pad test was associated with the lowest proportion of complete data (SISTEr: 85.1%, TOMUS: 88.3%) and approximately 1 in ten participants had missing voiding diaries at the time of primary outcome assessment. Generally, in both trials, a higher proportion of younger participants had missing data.

This analysis lacks a patient perspective regarding the reason for missing data that could have provided additional information regarding participant burden, motivations for adherence and study design. In addition, we were unable to compare the effect of the differential primary outcome assessment time-point within an identically designed trial.

Conclusions—Missing visits and data increased with time. Questionnaire data and physical outcome data (urinary stress test) that could be assessed during an in-person visit were least prone to missing data, whereas variables that required participant effort while away from the research team (pad test, voiding diary) were more likely to be missing. Older participants were more likely to provide complete data.

Keywords

Missing data; Urinary Incontinence; Clinical Outcomes; Surgical Trials; Primary Outcome Measures

Introduction

High quality clinical trial outcomes are characterized by sound study design, consistent collection of complete information, and appropriate statistical analyses. Missing data in clinical trials has received increasing attention recently as it presents distinct challenges for data analysis and interpretation [1] [2]. Strategies to reduce missing data should be considered prior to trial initiation; ongoing monitoring of missing data during recruitment is also recommended to proactively reduce missing data [1]. Despite the common occurrence of missing data in clinical trials there have been few detailed reports on the factors that may influence missingness. Of particular interest is missing outcome data as study power may be diminished and statistical methods to address this problem are inadequate. This study aims to report the frequency of missing primary outcome data, the reasons why the data were not obtained, and study participant factors associated with missingness in two large randomized clinical trials of surgery for stress urinary incontinence, the Stress Incontinence Surgical Treatment Efficacy Trial (SISTEr), comparing outcomes from the Burch colposuspension to the pubovaginal sling and the Trial of Midurethral Sling (ToMUS) study which compared outcomes between the retropubic and transobturator midurethral sling approaches.

Methods

The design and findings of SISTEr and TOMUS have been published previously [3–6]. All study participants provided written informed consent and the institutional review board at each participating site approved the study protocols. The primary outcome was assessed in SISTEr and TOMUS at 24 and 12 months respectively after surgery/randomization. The primary outcome for each trial was a composite measure which included the Medical, Epidemiologic and Social Aspects of Aging Project (MESA) questionnaire to quantify the self-reported components of stress incontinence [7,8], a self-completed 7 day voiding diary, urinary pad test and urinary stress test. The urinary pad test quantifies urine loss as measured by the weight of a perineal pad worn by the subjects during a standardized set of activities over a set period of time. We also collected data from the Incontinence Impact Questionnaire (IIQ) to evaluate the effect of incontinence on quality of life [7].

We assessed the proportion of women who completed each study visit and the reason for missing the visit data (i.e. missed visit, subject withdrawal from trial, refusal to provide data within an otherwise completed visit), as well as the pattern (timing) of missing data. If a woman was known to have met the definition of failure prior to the primary outcome visit, then her outcome data were complete for the time-to-event analysis even if she missed the primary outcome visit. A woman who did not meet the definition of failure prior to that visit and who did not attend the visit was censored at the last at which her outcome status was known. Retreatment was not a reason for withdrawal. Deaths were included in subjects lost to follow-up. Chi-square tests, Fisher's exact tests and t tests were used to compare the two groups (no missing vs. missing), as appropriate. In addition, we assessed the proportion of completeness for each component of the composite primary outcome variable. Analysis was performed using SAS Version 9.3 (SAS Institute, Cary, NC). A 5% two-sided significance level was used for all statistical testing.

Results

Table 1 displays the rates of follow-up in-person visits completed and reasons for missing by visit, demonstrating that visit attended rates decreased over time. A higher proportion of subjects attended all follow-up visits in the TOMUS trial (Table 2) and, overall, there was less missing data within the period that included collection of the primary outcome at 12 months.

At the time of primary outcome assessment, a similar proportion of participants completed their quality of life questionnaires (SISTEr: 95.5%, TOMUS: 97.8%). The highest proportion of completed data for the composite outcome variables was for the MESA questionnaire (SISTEr: 100%, TOMUS: 99.8%) and the urinary stress test (SISTEr: 96.1%, TOMUS: 96.7%). In both studies, the urinary pad test was associated with the lowest proportion of complete data (SISTEr: 85.1%, TOMUS: 88.3%) and approximately one in ten participants had missing voiding diaries (Table 3).

Table 4 displays the proportion of women who provided each component of the primary outcome at time of assessment. The proportion of women who provided all four components

was nearly twice as great in TOMUS (62.3%) compared to SISTEr: 35.7%), without major differences by surgical success status. A higher proportion of participants were censored prior to their primary outcome visit in SISTEr (20.6%) compared to TOMUS (6.0%).

In both trials, a higher proportion of younger participants had missing primary outcome data (Table 5). We also identified trial-specific associations; SISTEr participants with missing data were less likely to have had experienced adverse events and more likely to have had experienced surgical retreatment of stress urinary incontinence whereas TOMUS participants with missing data were more likely to have had fewer urinary incontinence episodes at baseline.

Discussion

The studies analyzed in this report experienced a relatively high rate of missing data involving the primary outcome composite measure. Our analysis quantified and corroborated the widely held belief that missing data increases over time. This finding may assist other clinical investigators in balancing the desire for long-term outcomes with the reality of missing data. Good clinical trial conduct places a high value on timely collection of all planned data, although a priority is typically placed on collection of primary outcome data.

It is possible that SISTEr follow-up was lower than in TOMUS due to the longer duration of follow-up in SISTEr, as it is harder to sustain follow-up compliance over a longer time period. Nevertheless even at the 12-month visit the SISTEr follow-up rate was slightly lower than the TOMUS rate. There is also likely an order effect, with the TOMUS trial following the SISTEr trial. The research teams are likely to have improved their skills in subject retention and their ability to improve data completeness.

Another reason for the differences between the two trials may be differences in eligibility criteria and morbidity of interventions. The SISTEr trial, which allowed concomitant abdominal surgery, was associated with a higher overall rate of adverse events compared to the subsequent TOMUS trial which did not allow concomitant abdominal surgery and used minimally invasive surgical techniques.

The use of composite outcome variables has advantages and disadvantages. Our findings that certain components of our composite outcome were more likely to be missing may inform other incontinence researchers regarding their choices to use these variables individually or within composite variables. Questionnaire data and physical finding data (urinary stress test) that could be assessed during a single visit were least prone to missing data, whereas variables that required participant activity while away from the research team (pad test, voiding diary) were more likely to be missing.

Our finding that younger participants were more likely to be associated with missing data adds weight to the need to include older participants in clinical research. Efforts to promote retention of younger subjects, while improving study adherence, may improve data completeness in this group. Older participants, in addition to broadening the generalizability

of research, appear to contribute complete data more reliably. This supports the national efforts to avoid ageism in research, especially for the elderly.

Despite the best efforts of the clinical research teams, missing data is likely to occur, requiring robust methods of analytic techniques to assess whether missingness is random. Our findings suggest that there may be demographic associations that require consideration to avoid unsound conclusions, including incorrect claims of treatment superiority that is due to differential drop-out. The National Academy encourages clinical trial investigators to consider proactive measures to reduce missing data in all participants, especially in these groups [1]. In addition to an on-going assessment of data quality, assessment of patterns of missingness may permit scientifically sound interventions that minimize missing data through the remainder of the trial.

The analytic approach to missing data is not uniform. Incomplete data can challenge the interpretation of trial outcomes, regardless of the analytic method used for missing data. Although we did not compare various analytic methods within these trials, the biostatistical literature is filled with cautionary guidance reminding investigators to assess whether missing data is occurring randomly or in patterns that may pose interpretation bias, limiting the impact of the trial itself.

Our analysis has several minor limitations, including a lack of patient perspective regarding the reason for missing data, which could have provided additional information regarding participant burden, motivation and study design. In addition, we were unable to compare the effect of the differential primary outcome assessment time-point within an identically designed trial, other surgical trials or other trials assessing other interventions, such as drugs, behavioral interventions or other incontinence treatments.

The findings from our analysis are strengthened by the high quality of trial designs, multi-site participation, sufficient participant retention and quality control for data management by an experienced coordinating center. These results may be used to inform regarding types of data and how it is collected in future trials regarding urinary incontinence.

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Table 1

Visit completion and reasons for missing by visit. N(%)

	SISTEr (n=655 randomized)				TOMUS (n=597 randomized)		
	6M	**12M**	**18M**	**24M**	**6M**	**12M**	**24M**
Visit attended	580 (88.5%)	532 (81.2%)	534 (81.5%)	510 (77.9%)	553 (92.6%)	539 (90.3%)	488 (81.7%)
Withdrew/refused/l.t.f.*	34 (5.2%)	62 (9.5%)	75 (11.5%)	116 (17.7%)	26 (4.4%)	48 (8.0%)	104 (17.4%)
Missed	41 (6.3%)	61 (9.3%)	46 (7.0%)	29 (4.4%)	18 (3.0%)	10 (1.7%)	5 (0.8%)

*lost to follow-up

Table 2

Pattern of missingness

	SISTEr (n=655 randomized)	TOMUS (n=597 randomized)
Primary outcome visit	24 months	12 months
Completed all FU visits	439 (67.0%)	523 (87.6%)
Completed primary outcome visit but missed 1 or more previous visits	71 (10.8%)	16 (2.7%)
Withdrew, refused or l.t.f.* prior to primary outcome visit	116 (17.7%)	48 (8.0%)
Missed primary outcome visit but not withdrawn, refused or l.t.f.*	29 (4.4%)	10 (1.7%)

*lost to follow-up

Table 3

Completeness of data among those who attended primary outcome visit

	SISTEr (24 months) (N=510)	TOMUS (12 months) (N=539)
IIQ completed	487 (95.5%)	527 (97.8%)
Measures for primary outcome completed		
MESA stress index	510 (100.0%)	538 (99.8%)
Voiding diary	450 (88.2%)	490 (90.9%)
Pad test	434 (85.1%)	476 (88.3%)
Stress test	490 (96.1%)	521 (96.7%)

Table 4

Completeness of primary outcome.

	SISTEr (n=655 randomized)	TOMUS (n=597 randomized)
Primary outcome visit:	24 months	12 months
Complete at primary outcome visit	234 (35.7%)	372 (62.3%)
Success[#]	185 (79.1%)[*]	309 (83.1%)[**]
Failure	49 (20.9%)[*]	63 (16.9%)[**]
Censored prior to primary outcome visit	135 (20.6%)	36 (6.0%)
Failed prior to primary outcome visit	286 (43.7%)	189 (31.7%)

[#]Success/Failure Definitions were study specific:

For the SISTEr study, overall success was defined as no self-reported symptoms of urinary incontinence, an increase of less than 15 g in pad weight during a 24-hour pad test, no incontinence episodes recorded in a 3-day diary, a negative urinary stress test (no leakage noted on examination during cough and Valsalva maneuvers at a standardized bladder volume of 300 ml), and no retreatment for urinary incontinence (including behavioral, pharmacologic, and surgical therapies). The definition of success specific to stress incontinence was limited to no self-reported symptoms of stress incontinence, a negative stress test, and no retreatment for stress incontinence.

The TOMUS study used a composite primary outcome, assessed at 12 months after randomization that included treatment success according to objective criteria and treatment success according to subjective criteria. The objective criteria were a negative provocative stress test, a negative 24-hour pad test, and no retreatment (behavioral, pharmacologic, or surgical) for stress incontinence; the subjective criteria were the absence of self-reported symptoms of stress-type urinary incontinence, as assessed with the use of the Medical, Epidemiological and Social Aspects of Aging questionnaire, no leakage recorded in a 3-day voiding diary, and no retreatment for stress incontinence.

[*] N=234 was used for the denominator.

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Table 5

Baseline Demographic and Baseline and Post-Surgery Clinical Characteristics by missingness status

	SISTEr			TOMUS		
Variable	**No missing at M24 (n=510)**	**Missing at M24 (n=145)**	**p-value** [3]	**No missing at M12 (n=539)**	**Missing at M12 (n=58)**	**p-value** [3]
Race/ethnicity			0.06			0.44
Hispanic	54 (10.6%)	18 (12.5%)		63 (11.7%)	8 (13.8%)	
Non-hispanic white	386 (75.7%)	94 (65.3%)		430 (79.8%)	43 (74.1%)	
Non-hispanic black	29 (5.7%)	15 (10.4%)		16 (3.0%)	1 (1.7%)	
Non-hispanic other	41 (8.0%)	17 (11.8%)		30 (5.6%)	6 (10.3%)	
Marital status			0.19			0.37
Married/living as married	356 (69.8%)	93 (64.1%)		375 (69.6%)	37 (63.8%)	
Not married or other	154 (30.2%)	52 (35.9%)		164 (30.4%)	21 (36.2%)	
Education			0.09			0.25
<High school	40 (7.8%)	14 (9.7%)		28 (5.2%)	7 (12.1%)	
High school	134 (26.3%)	37 (25.5%)		137 (25.4%)	12 (20.7%)	
>High school	194 (38.0%)	68 (46.9%)		195 (36.2%)	22 (37.9%)	
BA/BS	80 (15.7%)	18 (12.4%)		91 (16.9%)	10 (17.2%)	
Grad/prof	62 (12.2%)	8 (5.5%)		88 (16.3%)	7 (12.1%)	
Concomitant surgery			0.17			0.92
Yes	303 (59.4%)	77 (53.1%)		136 (25.2%)	15 (25.9%)	
No	207 (40.6%)	68 (46.9%)		403 (74.8%)	43 (74.1%)	
Treatment arm[1]			0.25			0.99
Group A	260 (51.0%)	66 (45.5%)		269 (49.9%)	29 (50.0%)	
Group B	250 (49.0%)	79 (54.5%)		270 (50.1%)	29 (50.0%)	
Any AE			0.03			0.12
Yes	314 (61.6%)	75 (51.7%)		234 (43.4%)	19 (32.8%)	
No	196 (38.4%)	70 (48.3%)		305 (56.6%)	39 (67.2%)	
Surgical retreatment[2]			0.004			0.66
Yes	15 (2.9%)	12 (8.3%)		14 (2.6%)	2 (3.4%)	
No	495 (97.1%)	133 (91.7%)		525 (97.4%)	56 (96.6%)	
Age	52.8 (10.1)	48.7 (10.4)	<.001	53.5 (10.7)	46.6 (11.5)	<.001

Variable	SISTEr			TOMUS		
	No missing at M24 (n=510)	Missing at M24 (n=145)	p-value [3]	No missing at M12 (n=539)	Missing at M12 (n=58)	p-value [3]
Average accidents/day	3.19 (3.03)	3.27 (2.80)	0.78	3.38 (3.04)	2.79 (2.26)	0.07
Total MESA score	25.8 (7.34)	25.7 (7.63)	0.82	25.7 (7.61)	24.7 (6.97)	0.36
Total IIQ	169.1 (100.1)	179.8 (105.2)	0.26	149.6 (97.2)	169.4 (97.8)	0.14
BMI	29.7 (5.87)	31.1 (6.90)	0.03	30.2 (6.56)	31.1 (8.17)	0.44

[1] Group A=Sling and Group B=Burch in SISTEr. Group A=RMUS and Group B=TMUS in TOMUS.

[2] Surgical retreatment included bulking agent injection, fascial or synthetic sling performed up to 24 months post study surgery for SISTEr and up to 12 months post study surgery for TOMUS.

[3] Chi-square or Fisher's exact test was used for categorical variables and two-sample *t* test was used for continuous variables.