LOCF Interval MMRM Approach to Missing Data

PSI Journal Club
Aug. 1, 2013

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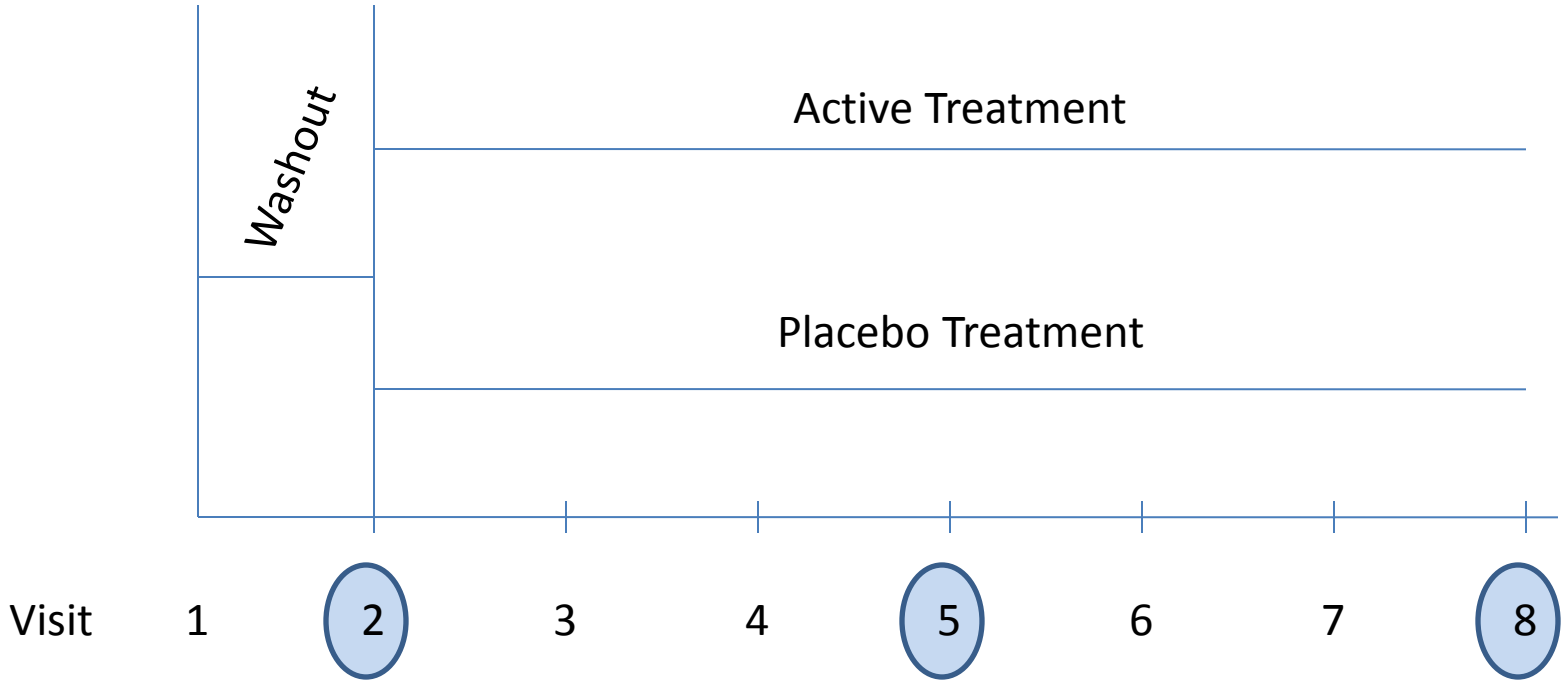
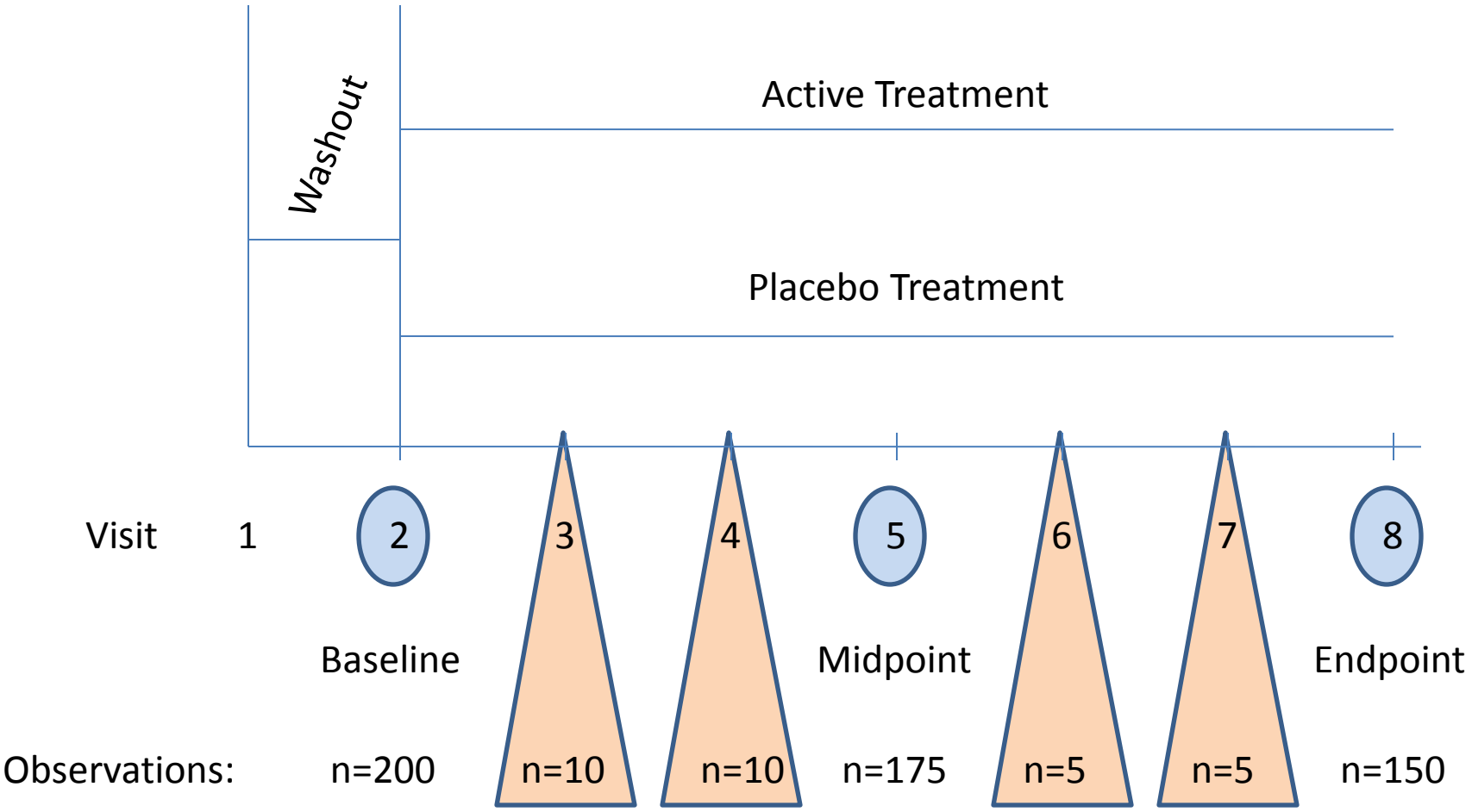
Example: Protocol-Specified Visits

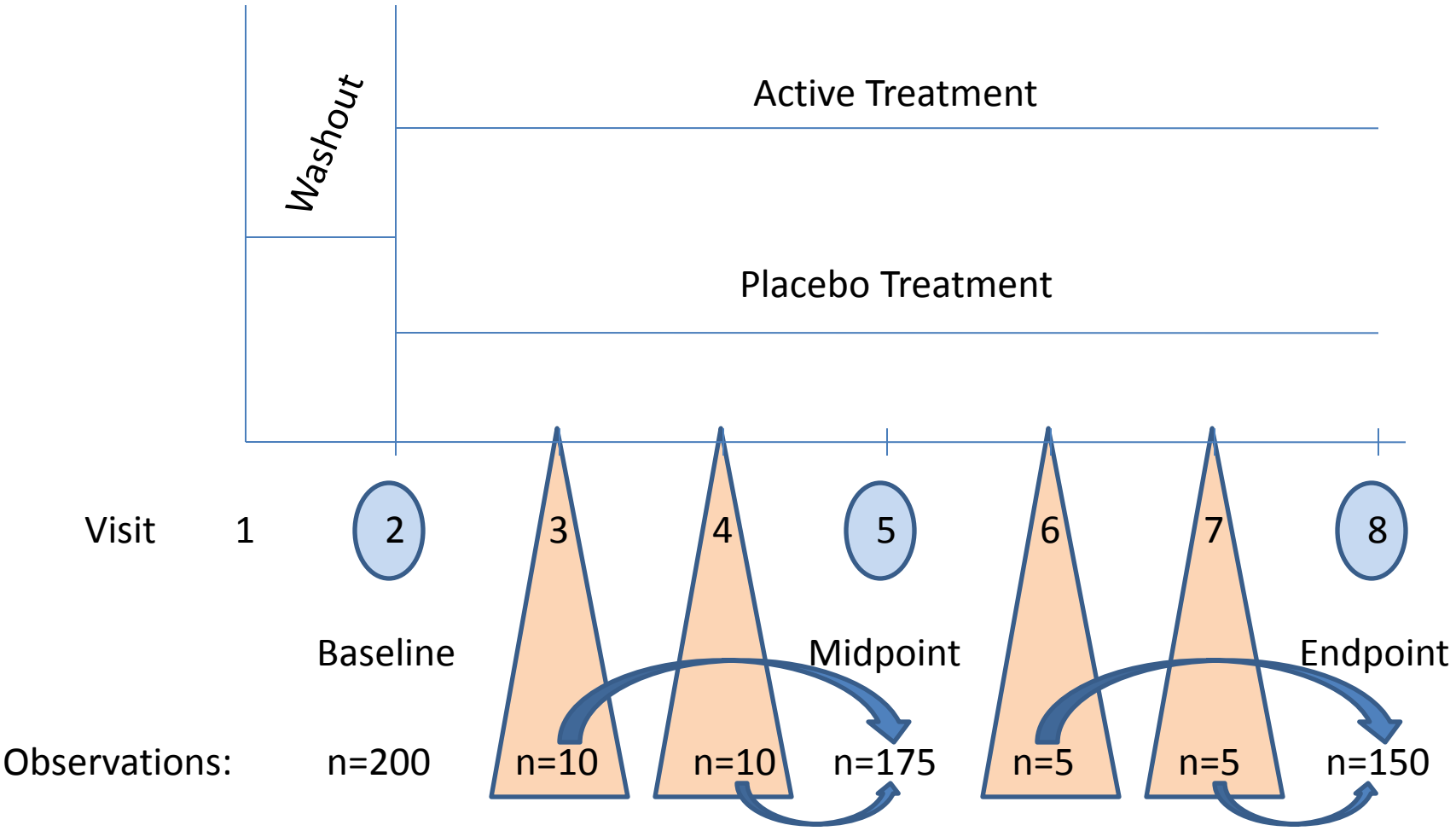


Observations: n=200 n=175 n=150

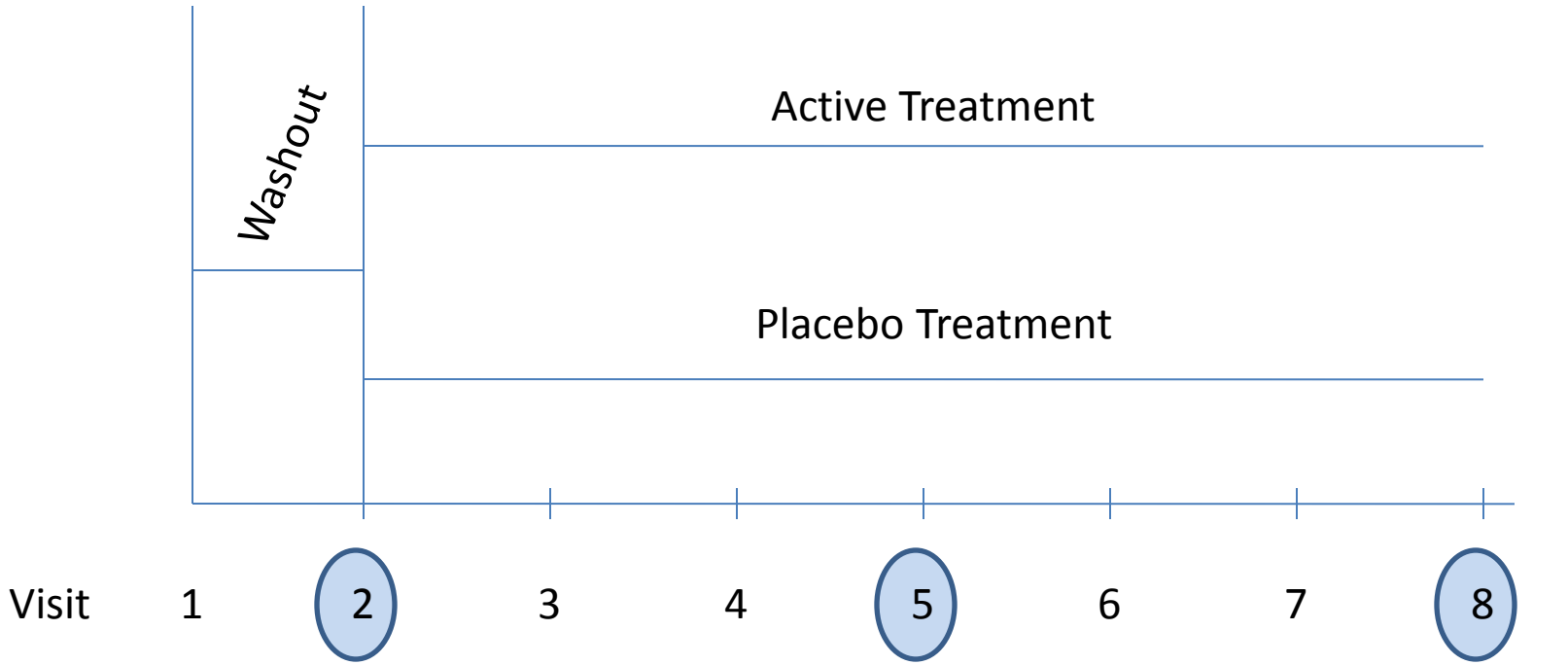
Example: All Visits



Example: Interval LOCF - MMRM

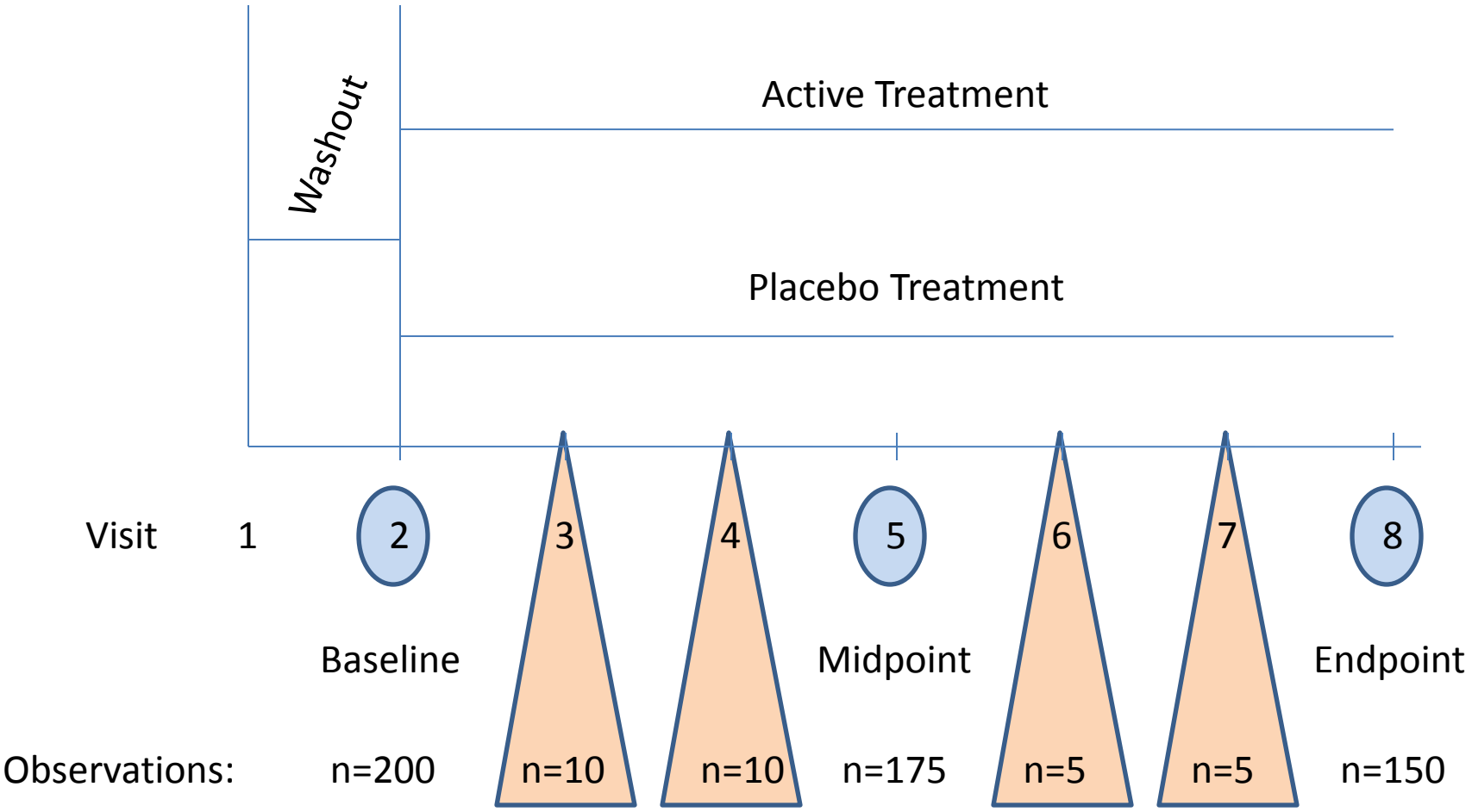


Example: Interval LOCF - MMRM

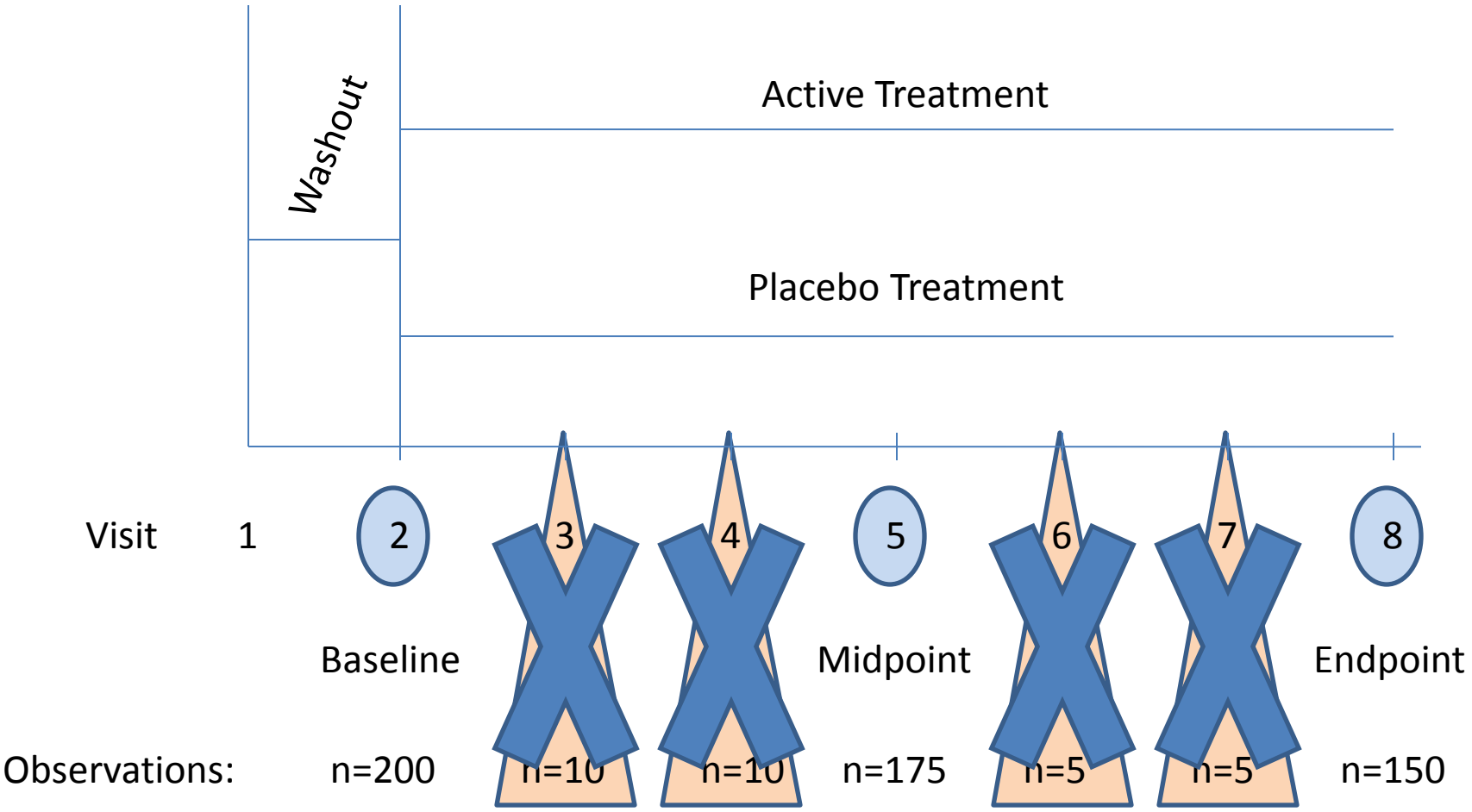


Observations: n=200 n=195 n=160

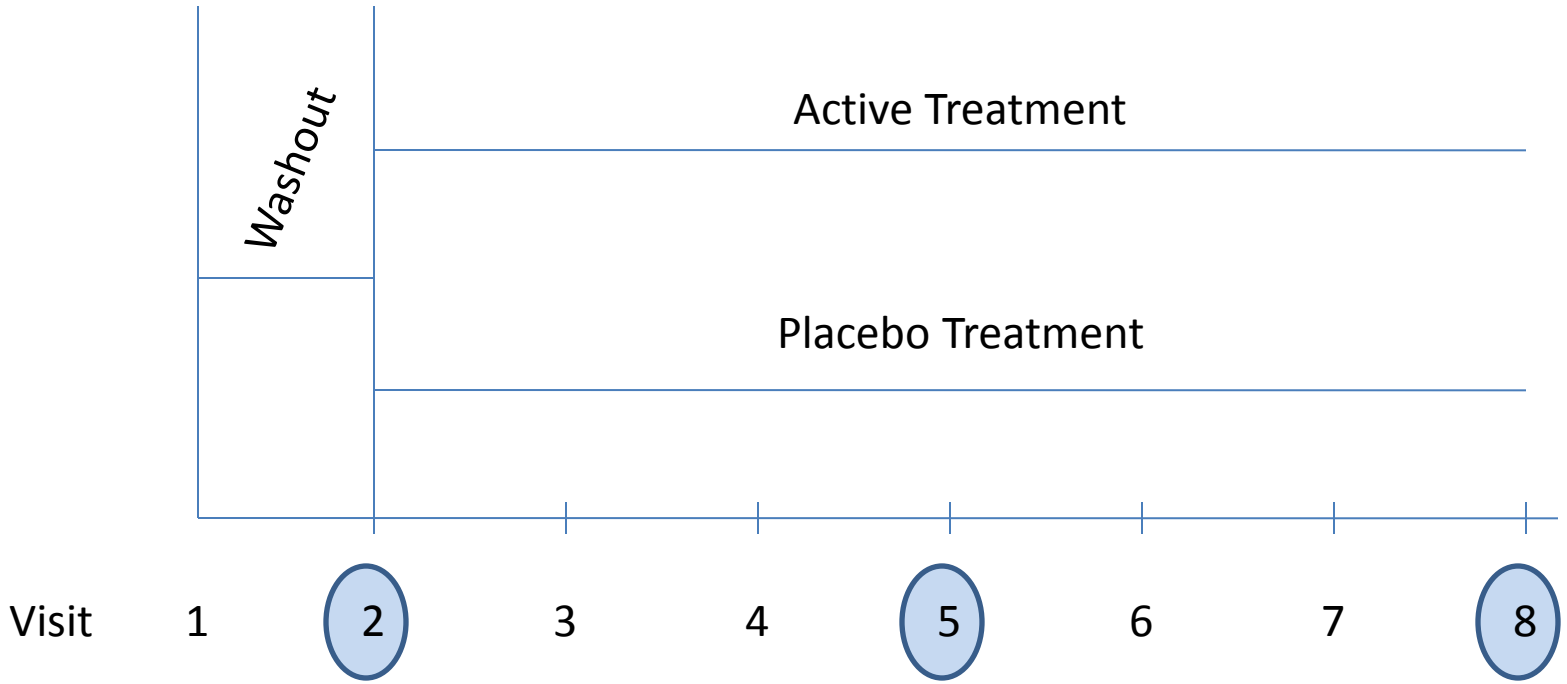
Example: All Visits



Example: Per Protocol Visits - MMRM

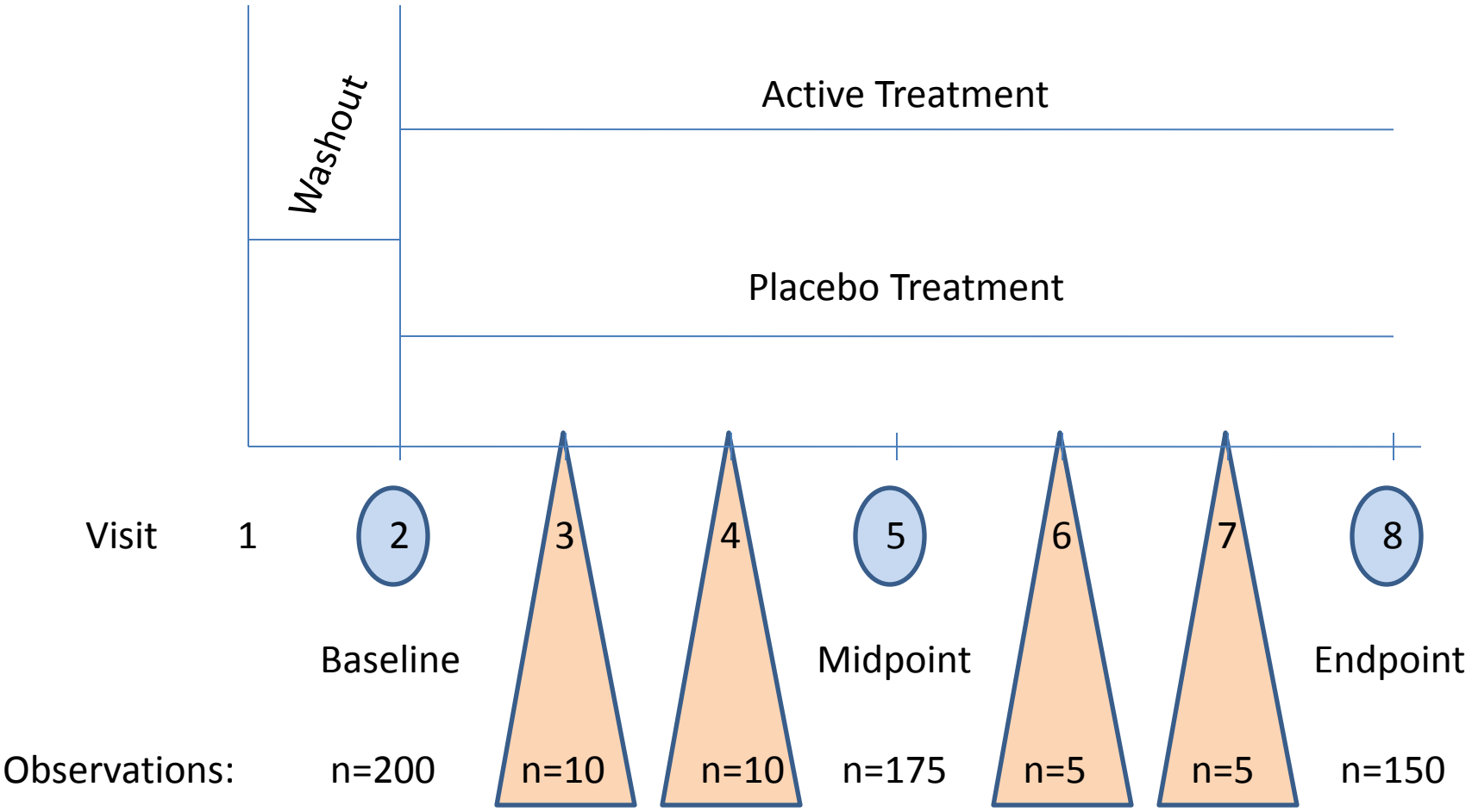


Example: Per Protocol Visits - MMRM

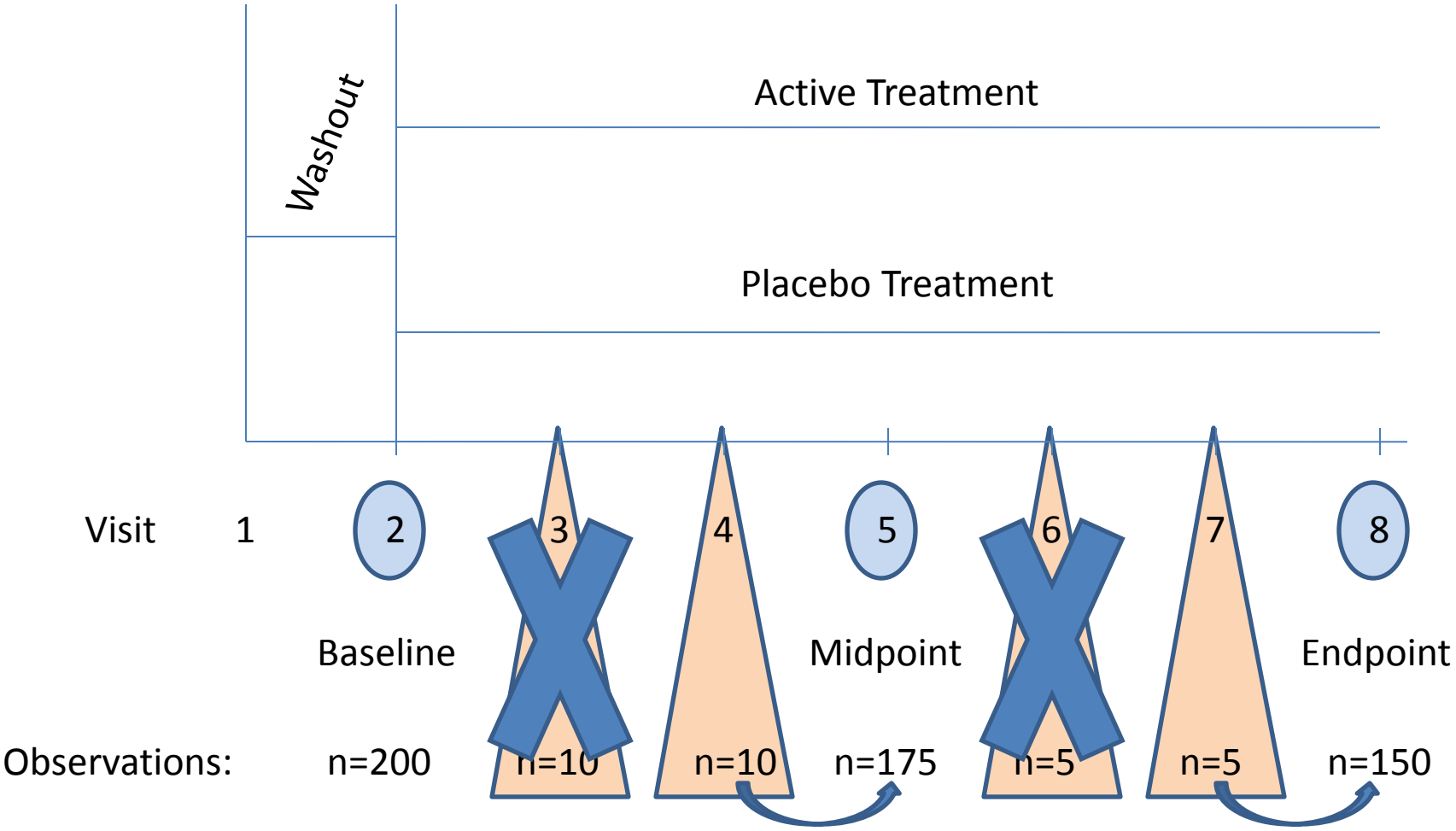


Observations: n=200 n=175 n=150

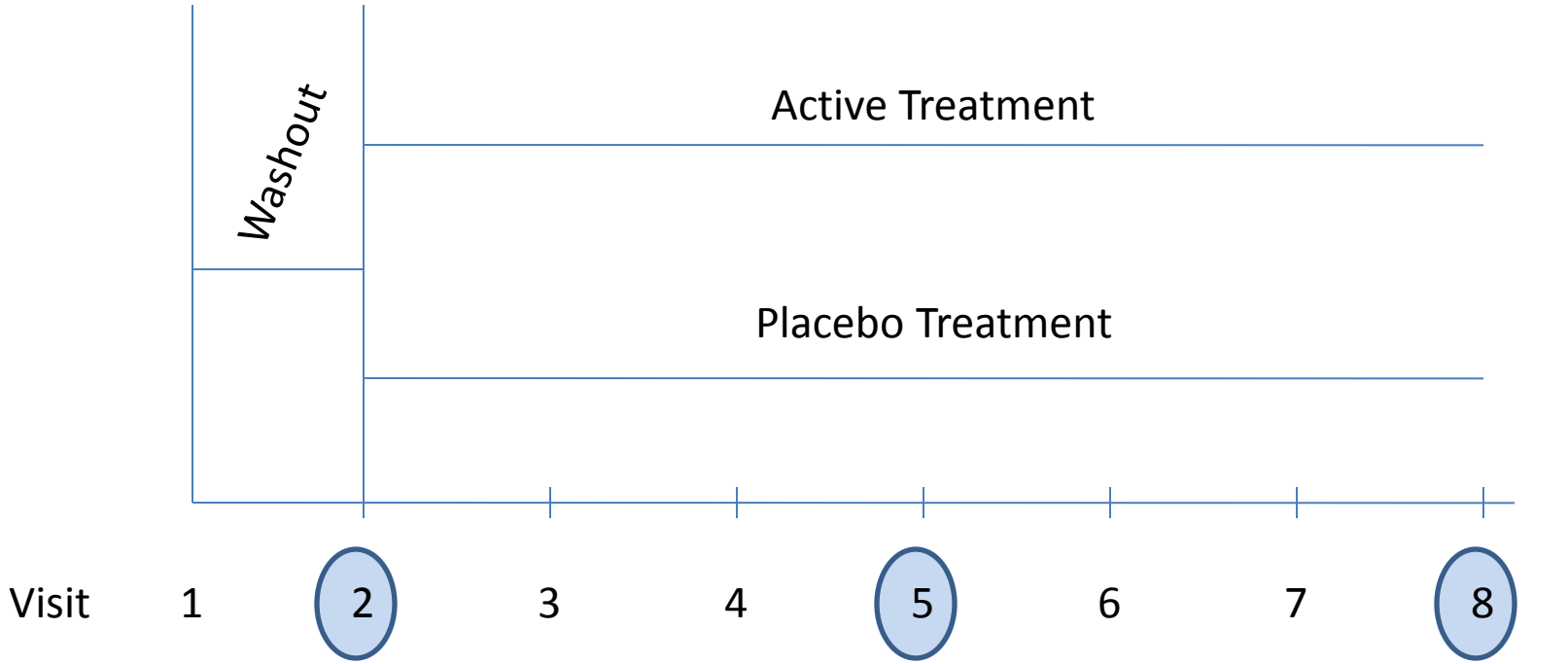
Example: All Visits



Example: Hybrid - MMRM

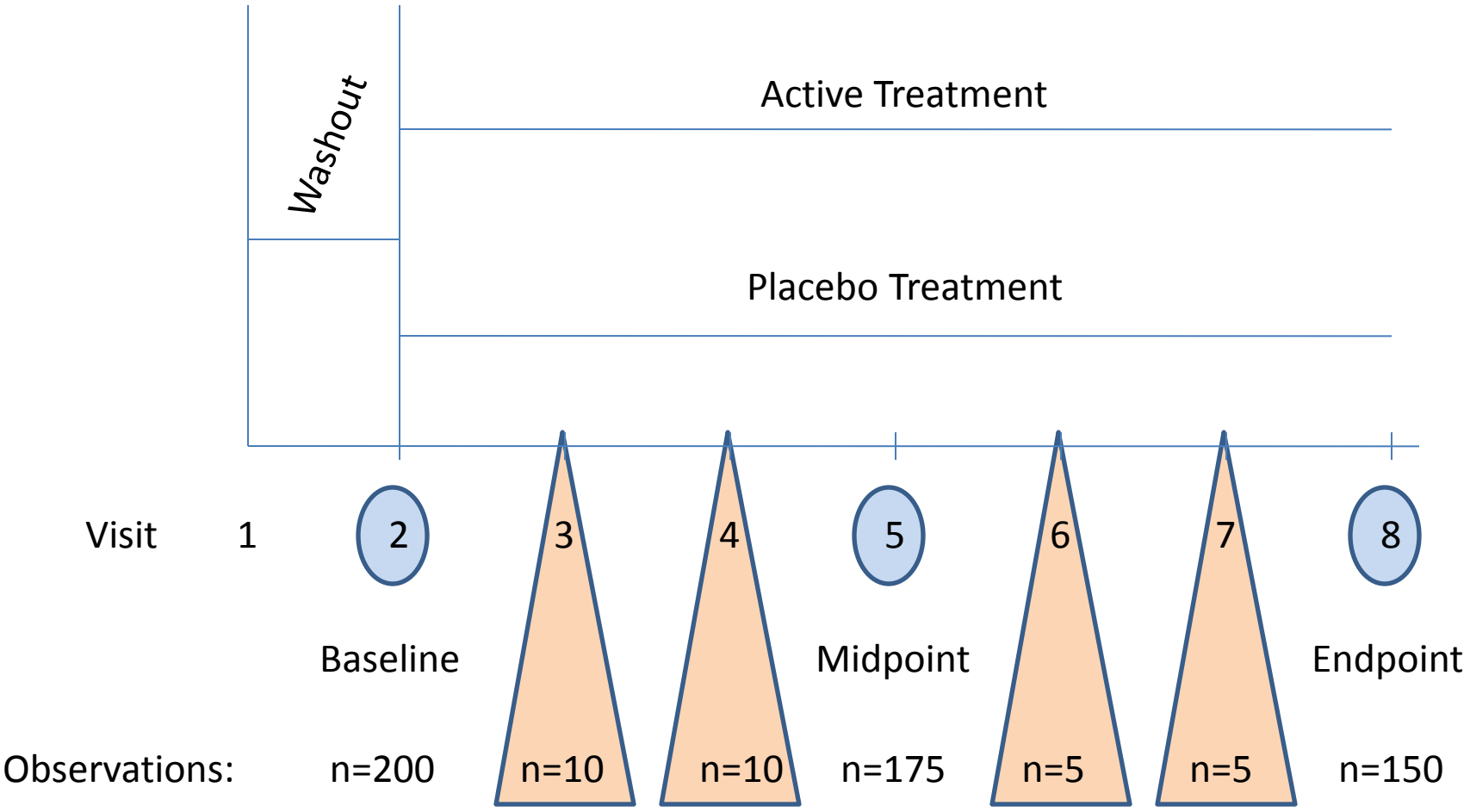


Example: Hybrid - MMRM

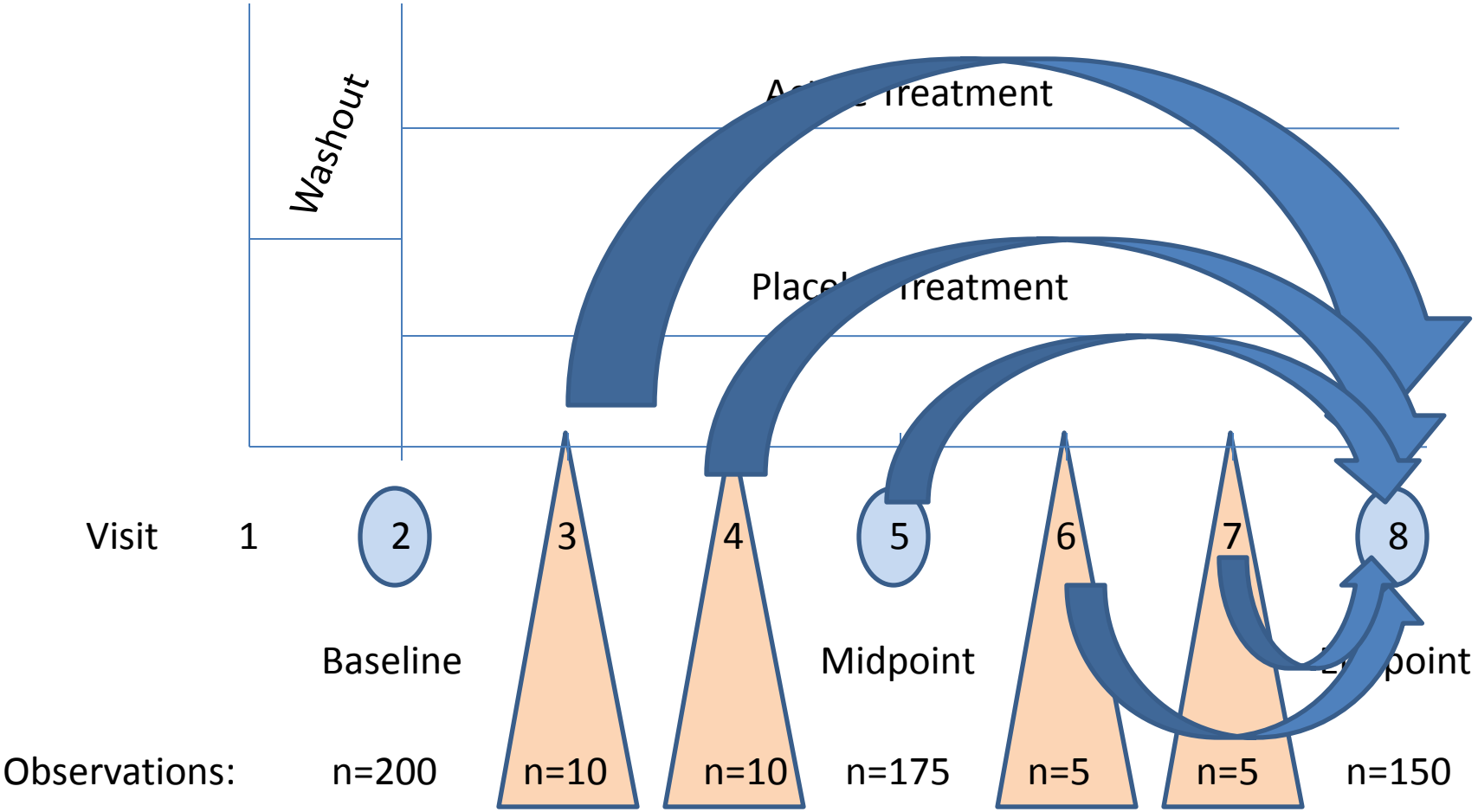


Observations: n=200 n=185 n=155

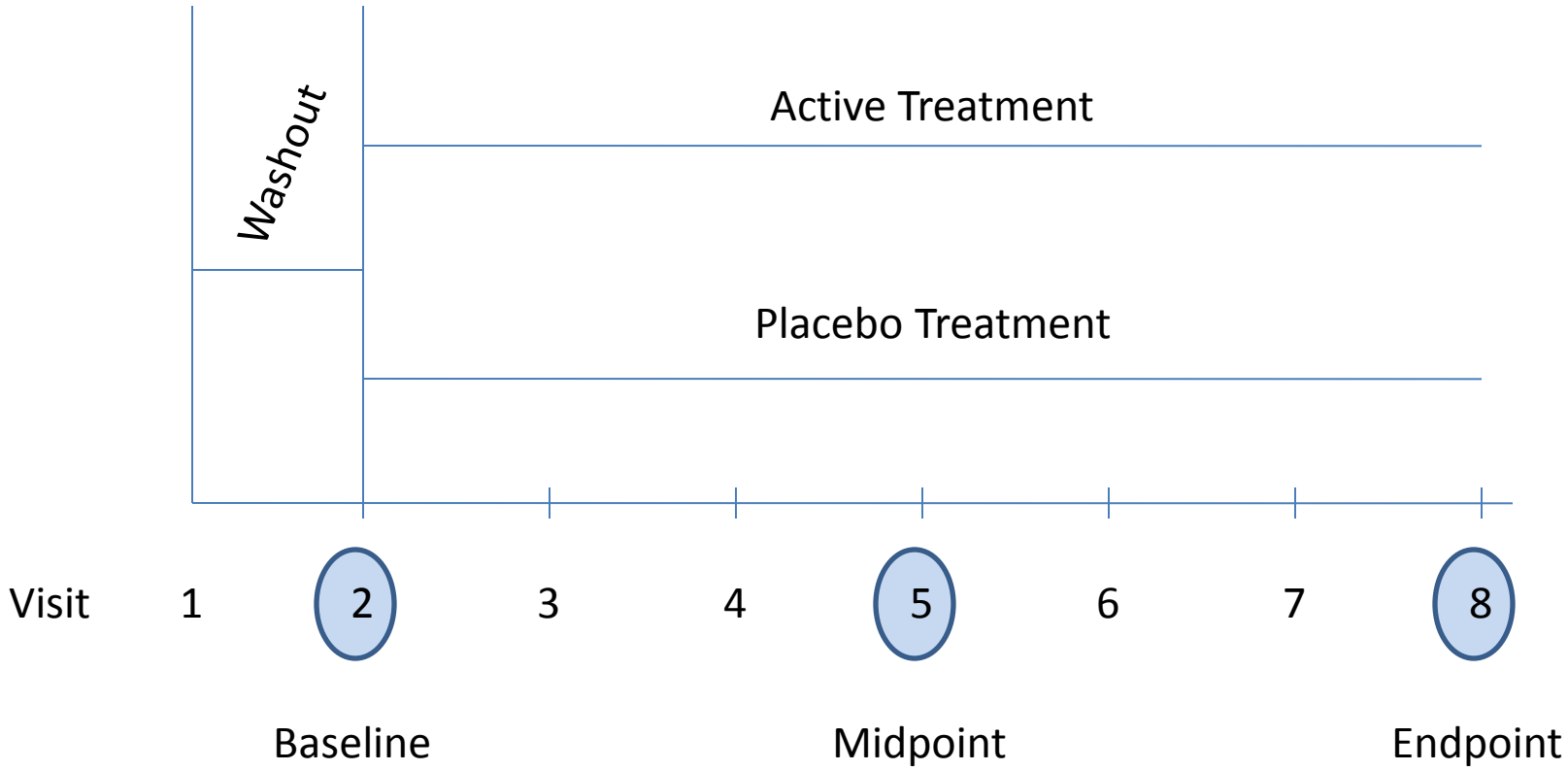
Example: All Visits



Example: LOCF

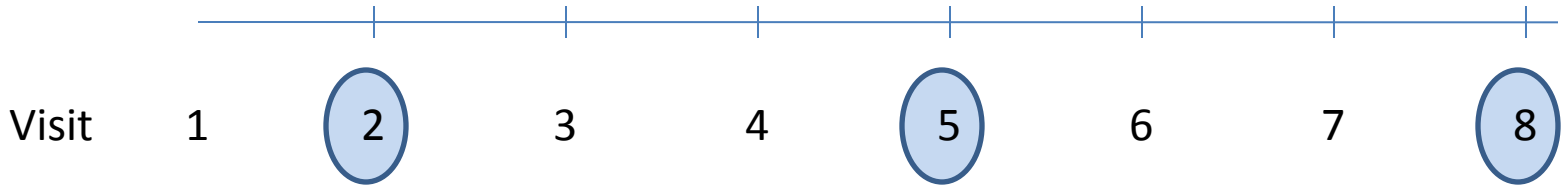


Example: LOCF



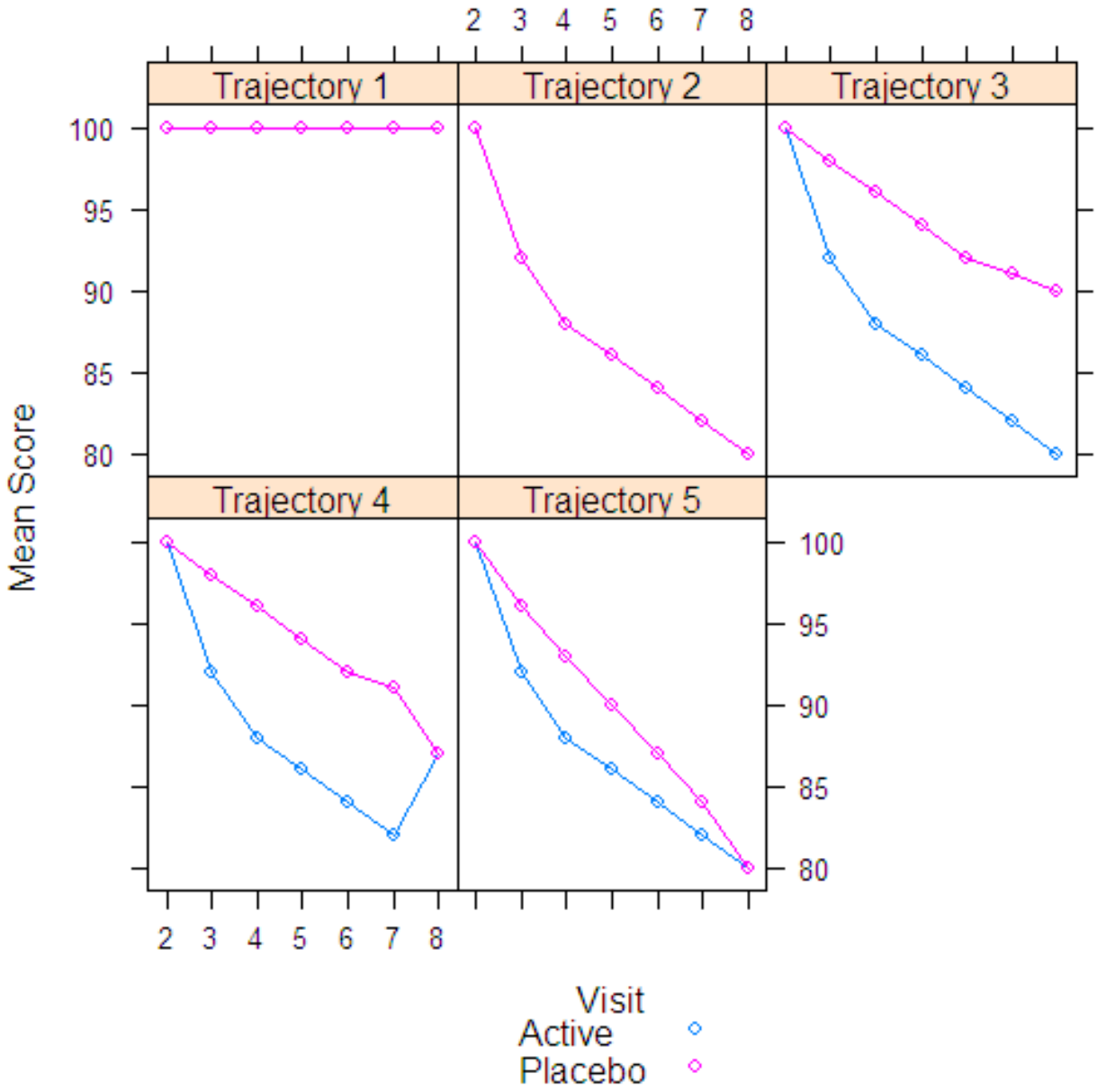
Observations: n=200 n=195

Example: Summary



	Baseline	Midpoint	Endpoint
Intrvl LOCF-MMRM	n=200	n=195	n=160
Per Protocol-MMRM	n=200	n=175	n=150
Hybrid-MMRM	n=200	n=185	n=155
LOCF:	n=200	NA	n=195

Figure 1 - Assumed Trajectories



Sim Parms – Data Collection & Missingness

Schedule of Events									
		Baseline		<-- Post-baseline -->					
Visit			2		3	4	5	6	7	8
Schedule A			X		X		X			X
Schedule B			X				X			X

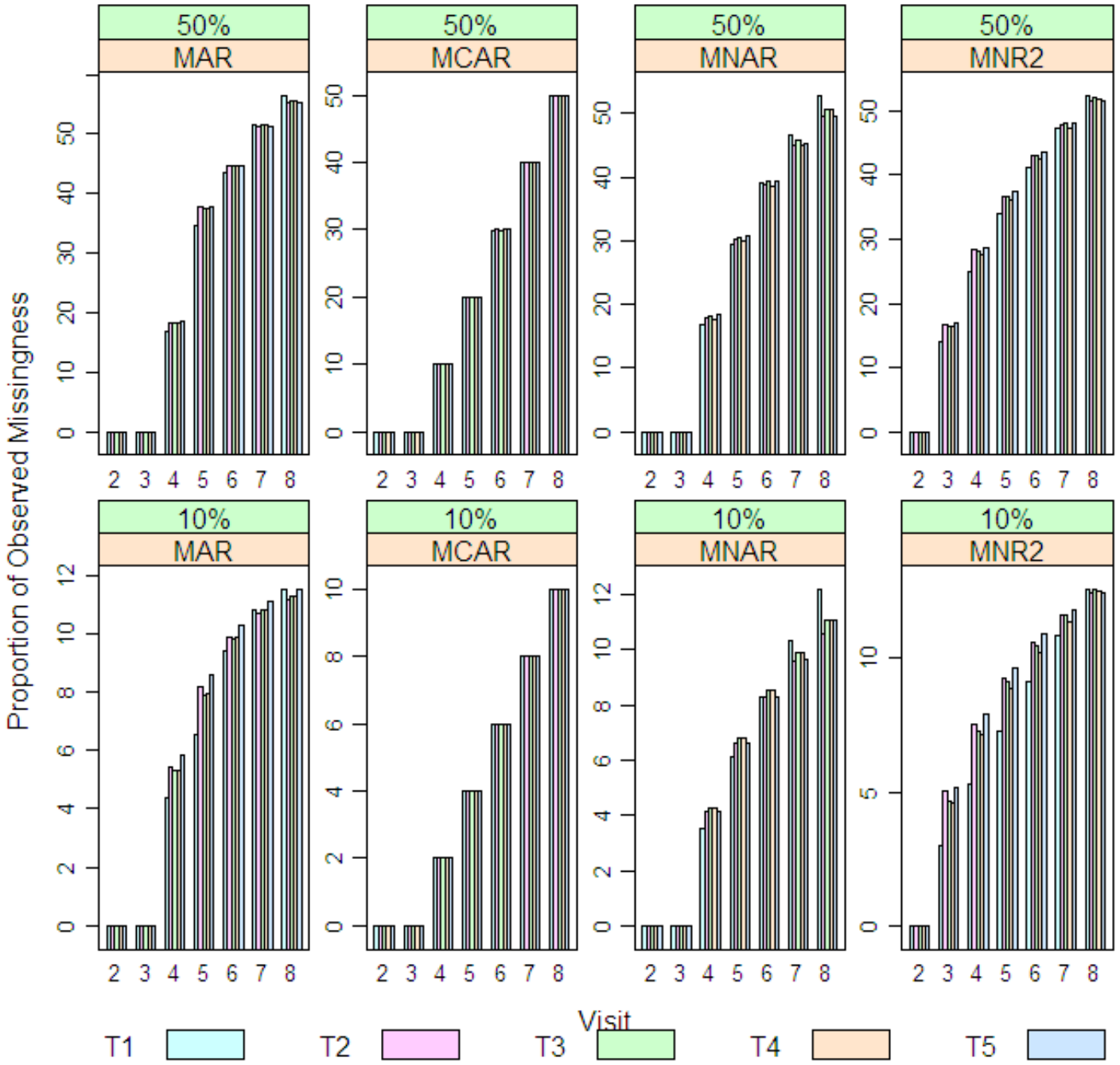
Amount missing

- 10%
- 50%

Missingness Assumption

- MCAR
- MAR
- MNAR – Schedule A
- MNR2 – Schedule B

Figure 2 - Percent Missing Data Patterns across Trajectories



Type I Error Rates (50% Missing)

Missingness Assumption	Trajectory	PP Visits MMRM	Hybrid MMRM	Interval LOCF MMRM	Benchmark LOCF
MCAR	1	4.84	4.68	5.16	5.02
	2	4.74	4.86	4.86	4.40
	4	5.04	6.54*	9.64*	23.8*
	5	5.04	5.28	5.32	8.12*
MAR	1	4.80	4.70	4.92	4.74
	2	5.08	4.96	5.30	5.10
	4	5.08	5.16	6.56*	32.6*
	5	5.34	5.30	6.02*	15.4*
MNAR	1	5.06	5.34	5.26	4.74
	2	4.80	5.00	5.16	5.22
	4	5.30	5.82	7.10*	29.1*
	5	4.98	5.20	5.18	12.5*
MNR2	1	4.96	5.18	5.12	5.04
	2	4.60	4.84	4.84	4.92
	4	4.94	4.68	6.18*	18.1*
	5	4.68	4.84	5.14	8.74*

denotes significance compared to 0.05, $p<0.05$.

* denotes McNemar's Test comparing to Per Protocol MMRM, $p<0.05$.

Type I Error Rates (10% Missing)

Missingness Assumption	Trajectory	PP Visits MMRM	Hybrid MMRM	Interval LOCF MMRM	Benchmark LOCF
MCAR	1	4.48	4.50	4.80	4.78
	2	5.44	5.46	5.36	5.28
	4	5.46	5.30	5.32	5.68
	5	5.12	5.06	4.92	5.00
MAR	1	4.98	4.94	4.92	4.68
	2	5.26	5.18	5.12	5.44
	4	5.34	5.36	5.32	7.70*
	5	5.08	5.20	5.14	6.12*
MNAR	1	5.08	5.12	5.04	4.80
	2	5.02	5.22	5.16	5.08
	4	4.74	5.04	5.00	6.80*
	5	5.04	5.10	5.30	6.82*
MNR2	1	5.60	5.38	5.30	5.38
	2	5.36	5.26	5.26	5.16
	4	5.00	4.88	4.78	5.70*
	5	5.28	5.20	5.22	5.16

denotes significance compared to 0.05, $p<0.05$.

* denotes McNemar's Test comparing to Per Protocol MMRM, $p<0.05$.

Bias Assessment (50%)

Missingness Assumption	Trajectory	PP Visits MMRM	Hybrid MMRM	Interval LOCF MMRM	Benchmark LOCF
MCAR	1	0.02	0.03	0.06	0.05
	2	-0.05	-0.07	-0.05	-0.03
	3	**-0.16**	**-0.29**	**-0.65**	**-1.17**
	4	0.05	**1.51**	**2.32**	**3.94**
	5	0.01	**0.44**	**0.82**	**1.83**
MAR	1	-0.10	-0.11	-0.10	-0.08
	2	-0.03	-0.03	-0.03	-0.05
	3	-0.06	0.03	**-0.18**	**-0.87**
	4	-0.02	**0.78**	**1.62**	**4.47**
	5	-0.01	**0.39**	**0.96**	**2.86**

Note: favors active
favors placebo

Bias Assessment (50%)

Missingness Assumption	Trajectory	PP Visits MMRM	Hybrid MMRM	Interval LOCF MMRM	Benchmark LOCF
MNAR	1	0.01	0.02	0.01	-0.02
	2	0.02	0.05	0.05	0.04
	3	**-0.65**	**-0.30**	**-0.29**	**-0.57**
	4	**-0.24**	**0.80**	**1.68**	**4.40**
	5	-0.06	**0.25**	**0.73**	**2.59**
MNR2	1	-0.07	-0.06	-0.04	-0.01
	2	0.08	0.06	0.03	-0.01
	3	**-0.56**	**-0.30**	**-0.29**	**-0.46**
	4	**-0.25**	**0.60**	**1.34**	**3.65**
	5	-0.09	**0.21**	**0.61**	**2.15**

Note: favors active
favors placebo

Bias Assessment (10%)

Missingness Assumption	Trajectory	PP Visits MMRM	Hybrid MMRM	Interval LOCF MMRM	Benchmark LOCF
MCAR	1	**-0.11**	**-0.11**	**-0.11**	**-0.11**
	2	0.03	0.04	0.04	0.05
	3	0.08	0.05	-0.03	**-0.16**
	4	-0.01	**0.19**	**0.33**	**0.78**
	5	0.01	0.07	**0.12**	**0.35**
MAR	1	0.01	0.00	0.00	0.00
	2	0.05	0.05	0.05	0.04
	3	-0.10	-0.03	**0.12**	**0.60**
	4	0.05	**0.16**	**0.39**	**1.71**
	5	-.01	0.09	**0.27**	**1.21**

Note: favors active
favors placebo

Bias Assessment (10%)

Missingness Assumption	Trajectory	PP Visits MMRM	Hybrid MMRM	Interval LOCF MMRM	Benchmark LOCF
MNAR	1	-0.03	-0.02	-0.01	-0.01
	2	-0.02	-0.03	-0.03	-0.04
	3	**-0.95**	**-0.68**	**-0.40**	**0.19**
	4	**-0.46**	**-0.27**	**0.15**	**1.42**
	5	**-0.12**	-0.04	**0.16**	**1.03**
MNR2	1	0.03	0.03	0.04	0.04
	2	-0.01	-0.02	-0.02	-0.02
	3	**-0.74**	**-0.50**	**-0.26**	**0.19**
	4	**-0.37**	**-0.21**	**0.13**	**1.07**
	5	**-0.10**	-0.05	0.09	**0.68**

Note: favors active
favors placebo

SE of Estimates at Visit 8

50% Missing

Missing Data Model	PP Visits	Hybrid	Interval LOCF	Benchmark
MCAR	4.81	4.34	3.98	3.15
MAR	5.25	4.89	4.43	2.99
MNAR	4.76	4.52	4.29	3.13
MNR2	4.85	4.64	4.45	3.51

10% Missing

Missing Data Model	PP Visits	Hybrid	Interval LOCF	Benchmark
MCAR	3.66	3.62	3.58	3.44
MAR	3.70	3.68	3.66	3.57
MNAR	3.55	3.55	3.55	3.48
MNR2	3.59	3.60	3.60	3.56

Conclusions

- Per Protocol MMRM was superior
- LOCF Interval MMRM led to biases
- When writing phase 3/4 protocols, use Per Protocol Visits MMRM

Acknowledgements

- Brian Millen
- Lingling (Jennifer) Xie
- Fangyi Zhao
- Craig Mallinckrodt

References

- National Research Council (2010). The Prevention and Treatment of Missing Data in Clinical Trials. Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, Division of behavioral and Social Sciences and Education. Washington DC. The National Academies Press.
- Mallickrodt C, Kaiser C, Watkin J, Detke M, Molenberghs G, and Carroll R. "Type I error rates from likelihood-based repeated measures and analyses of incomplete longitudinal data." *Pharmaceut. Statist.* 2004; 3: 171–186.
- Mallinckrodt, Craig H. , Clark, W. Scott and David, Stacy R.(2001) 'Accounting for Dropout Bias Using Mixed-Effects Models', *J Biopharm Stat*, 11: 1, 9 — 21.
- Lane P. Handling drop-out in longitudinal clinical trials: a comparison of the LOCF and MMRM approaches. *Pharmaceut. Statist.* 2008; 7: 93–106.
- Mallinckrodt C., Kaiser C., Watkin J., Molenberghs G., and Carroll R. The effect of correlation structure on treatment contrasts estimated from incomplete clinical trial data with likelihood-based repeated measures compared with last observation carried forward ANOVA. *Clinical Trials* 2004; 1: 477-489.

References (cont.)

- Gueorguieva, R., & Krystal, J. H. (2004). Move over ANOVA: Progress in analyzing repeated-measures data and its reflection in papers published in the archives of general psychiatry. Archives of General Psychiatry, 61(3), 310-317.
- Siddiqui O, Hung J, O'Neill R: MMRM vs. LOCF: a comprehensive comparison based on simulation study and 25 NDA datasets. J Biopharm Stat 2009; 19:227–246.
- Fisher LD, Dixon DO, et al. Intention-to-Treat in clinical trials, in KE Peace (Ed.), Statistical Issues in Drug Research and Development. Marcel Dekker, 1990.
- Molenberghs G, Thijs H, Jansen I, et al. Analyzing incomplete longitudinal clinical trial data. Biostatistics. 2004;5:445–464.
- Shao J, Zhong B. Last observation carry-forward and last observation analysis. Stat Med. 2003;22: 2429–2441.
- Mallinckrodt C., Lane P., Schnell D., Peng Y., and Mancuso J. Recommendations for the Primary Analysis of Continuous Endpoints in Longitudinal Clinical Trials. Drug Information Journal 2008; 42: 303-19.
- European Medicines Agency (EMEA) Guideline on Missing Data in Confirmatory Clinical Trials released April 2009 (CPMP/EWP/1776/99 Rev. 1 Corr).

BACK-UP SLIDES

Type I Error Rates (30% Missing)

Missingness Assumption	Trajectory	PP Visits MMRM	Hybrid MMRM	Interval LOCF MMRM	Benchmark LOCF
MCAR	1	4.86	4.76	4.76	4.68
	2	4.48	4.52	4.78	4.28
	4	4.88	5.14	5.74*	10.5*
	5	5.66	5.30	5.14*	5.92
MAR	1	4.84	4.58	4.50	4.64
	2	4.88	4.90	5.34	4.90
	4	4.76	5.24	6.50*	11.7*
	5	4.66	5.04	5.54*	6.56*
MNAR	1	4.76	4.96	5.10	5.18
	2	4.68	4.82	4.88	4.96
	4	5.30	5.04	5.54	17.5*
	5	4.80	4.42	4.76	9.48*
MNR2	1	4.82	4.98	4.98	5.08
	2	4.50	4.58	4.62	4.64
	4	5.10	4.78	5.58	16.4*
	5	4.66	4.54	4.84	8.60*

denotes significance compared to 0.05, $p<0.05$.

* denotes McNemar's Test comparing to Per Protocol MMRM, $p<0.05$.

SE of Estimates at Visit 8

30% Missing

Missing Data Model	PP Visits	Hybrid	Interval LOCF	Benchmark
MCAR	4.11	3.92	3.76	3.31
MAR	4.18	3.95	3.72	3.30
MNAR	3.99	3.92	3.86	3.34
MNR2	4.01	3.93	3.86	3.34

Bias Assessment (30%)

Missingness Assumption	Trajectory	PP Visits MMRM	Hybrid MMRM	Interval LOCF MMRM	Benchmark LOCF
MCAR	1	-0.00	-0.00	0.03	0.03
	2	0.01	-0.01	-0.01	-0.01
	3	**-0.13**	**-0.20**	**-0.34**	**-0.76**
	4	0.02	**0.72**	**1.26**	**2.38**
	5	0.02	**0.22**	**0.43**	**1.11**
MAR	1	-0.03	-0.00	0.02	0.01
	2	**0.12**	**0.12**	0.08	0.07
	3	0.03	-0.06	**-0.30**	**-0.66**
	4	-0.01	**0.81**	**1.40**	**2.53**
	5	0.03	**0.28**	**0.53**	**1.22**

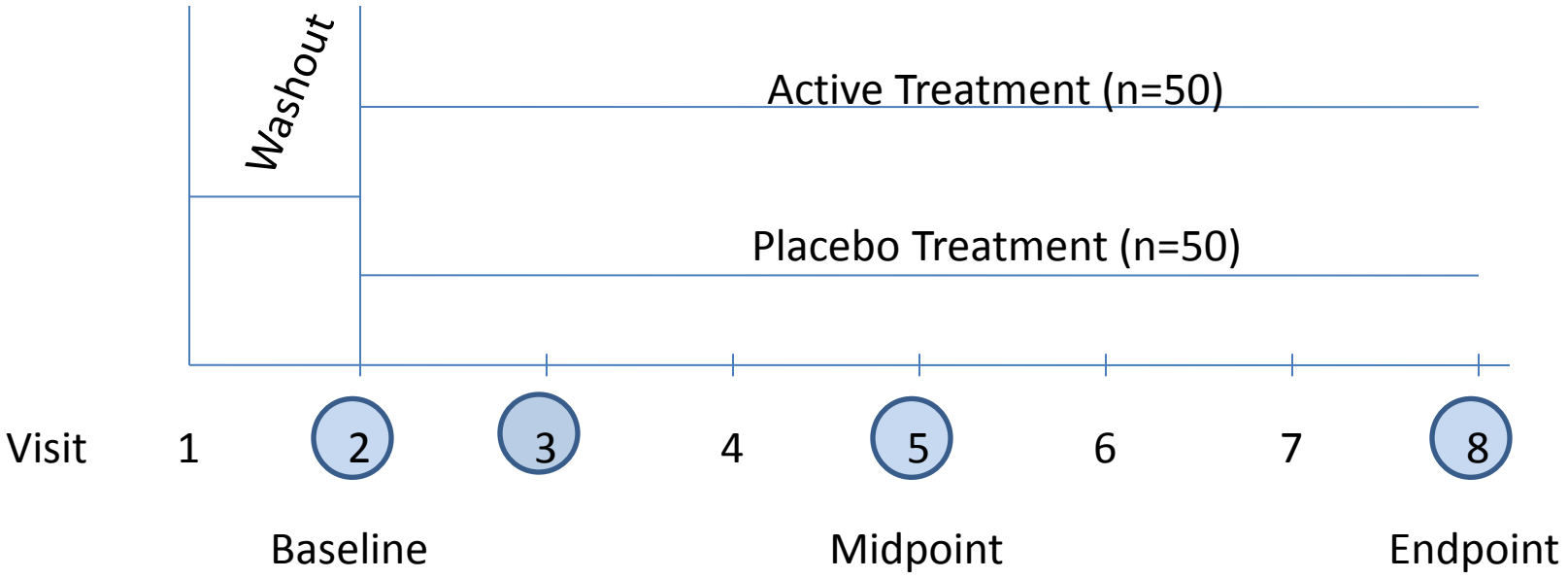
Note: favors active
favors placebo

Bias Assessment (30%)

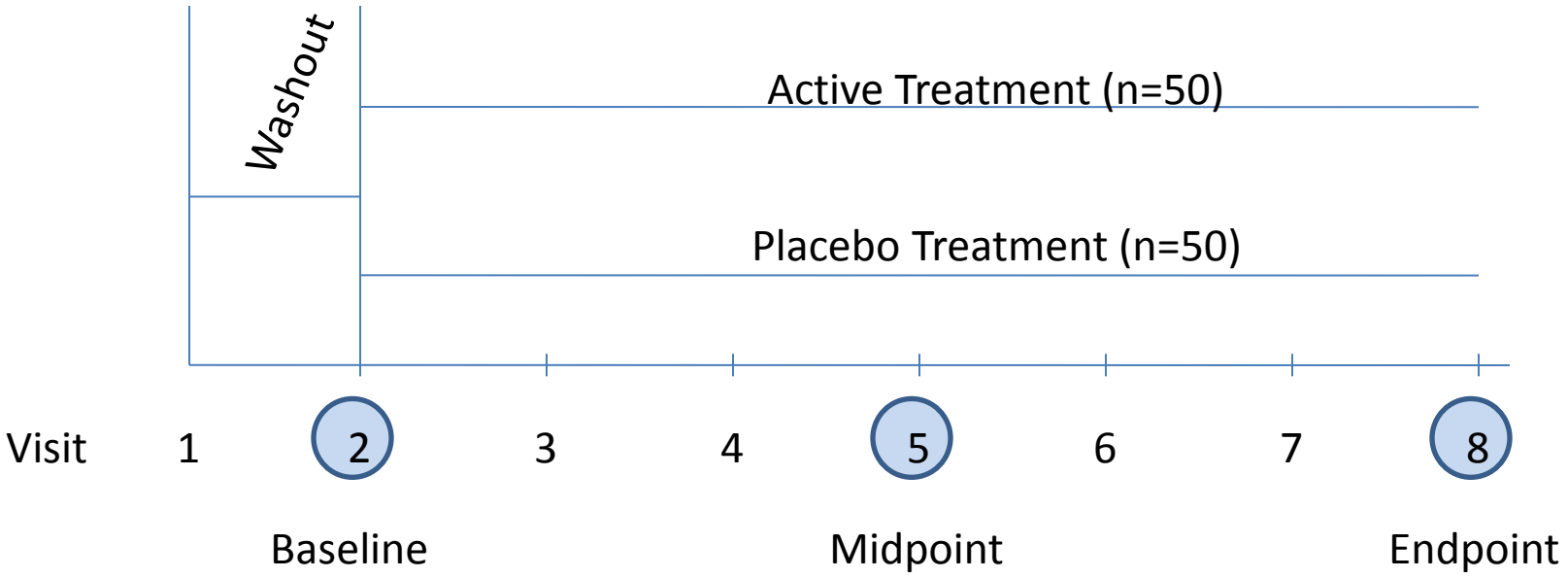
Missingness Assumption	Trajectory	PP Visits MMRM	Hybrid MMRM	Interval LOCF MMRM	Benchmark LOCF
MNAR	1	-0.02	-0.02	0.01	-0.02
	2	0.04	0.04	0.05	0.04
	3	**-1.23**	**-0.74**	**-0.46**	**-0.57**
	4	**-0.66**	-0.03	**0.69**	**3.28**
	5	**-0.34**	**-0.13**	0.09	**2.19**
MNR2	1	-0.06	-0.06	-0.03	-0.01
	2	-0.01	-0.02	-0.04	-0.01
	3	**-1.08**	**-0.63**	**-0.39**	-0.01
	4	**-0.52**	0.09	**0.80**	**3.17**
	5	**-0.29**	-0.06	**0.17**	**1.96**

Note: favors active
favors placebo

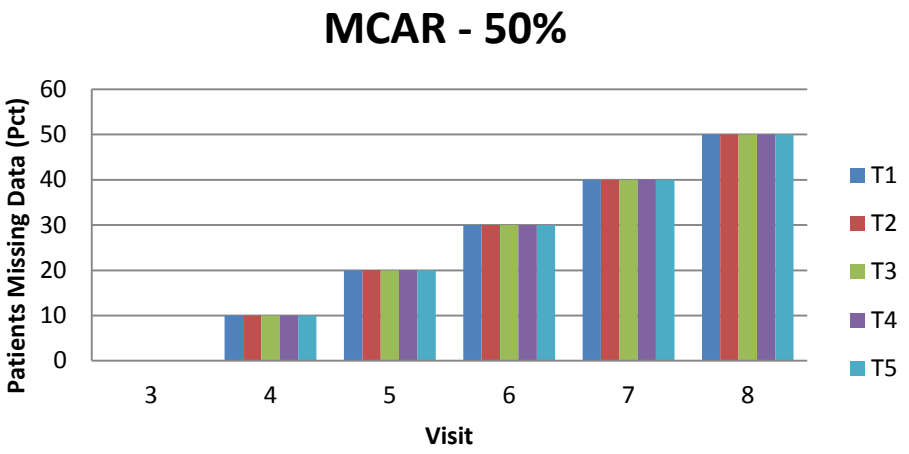
Simulation Parameters

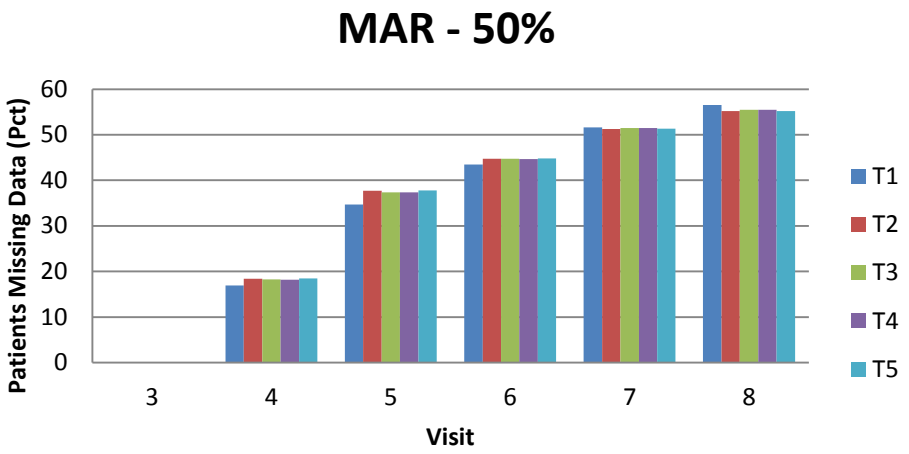


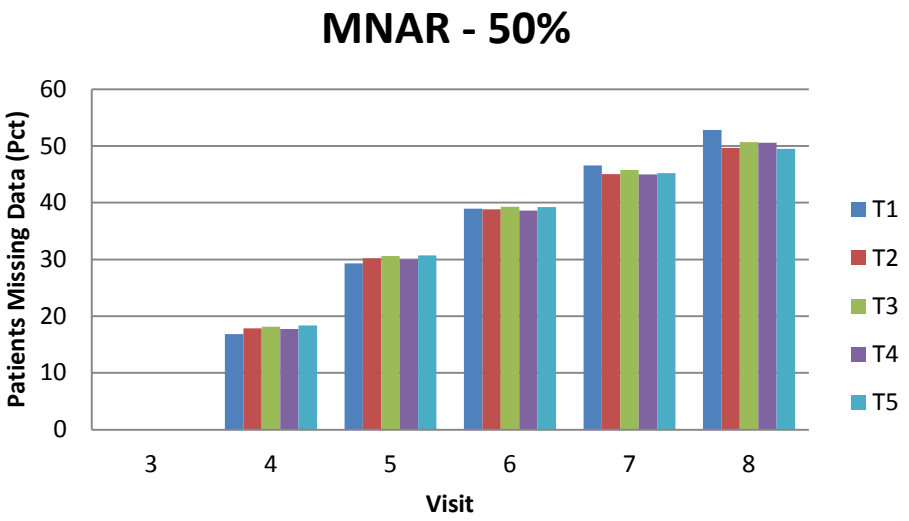
Simulation Parameters

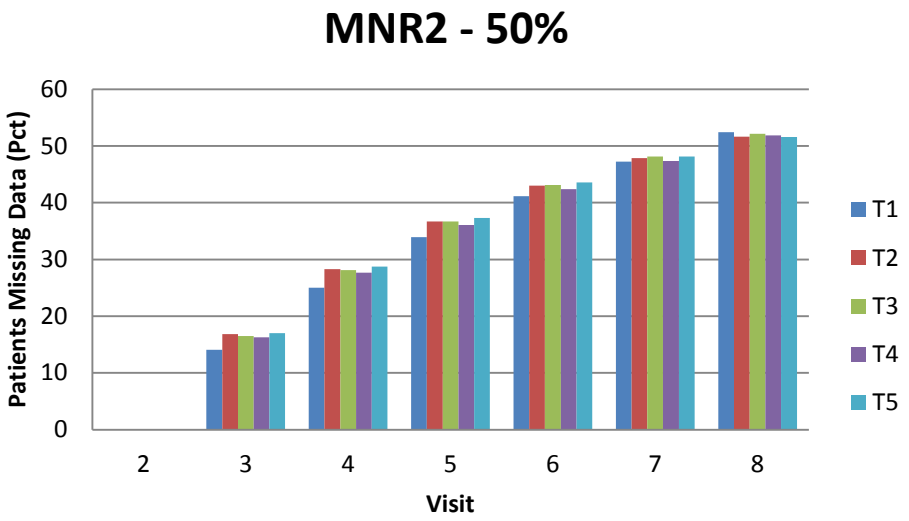


Missing Data Patterns









Sim Parameters – Error (Co)variance

300	330	310	280	250	230	210
330	**400**	360	320	290	260	240
310	360	**410**	360	320	290	260
280	320	360	**420**	360	320	290
250	290	320	360	**430**	360	320
230	260	290	320	360	**440**	360
210	240	260	290	320	360	**450**

Mallinckrodt and Kaiser (2004). "Type I error rates from likelihood-based repeated measures analyses of incomplete longitudinal data." *Pharmaceut. Statist.* 2004; 3: 171-186.

Sim Parameters – Correlation Matrix

Visit	1	2	3	4	5	6	7
1	1.000						
2	0.953	1.000					
3	0.884	0.889	1.000				
4	0.789	0.781	0.868	1.000			
5	0.696	0.699	0.762	0.847	1.000		
6	0.633	0.620	0.683	0.744	0.828	1.000	
7	0.572	0.566	0.605	0.667	0.727	0.809	1.000
Variance	300	400	410	420	430	440	450

Sim Parameters – Computing Details

- PC-SAS 9.1+ needed for RANDGEN function to simulate multivariate normal distribution

- 5,000 simulations of each missingness model (4), missingness amount (2), trajectory (5), and (co)variance structure (3) resulted in 600,000 total simulations

Missingness Logistics – MCAR

- Scale results simulated for visits 2-8
- Early dropout visit assigned to each patient ~UNIF(4,8)
- First x% (10 or 50) were considered early DC’ers
- Scale results kept for visits 2,3,5,8 and endpt.

Missingness Logistics – MAR

- Scale results simulated for visits 2-8
- Each pt's worst score used to create distribution and threshold
- Pt's score at V3 compared to threshold and probability of being missing at V4 (p4) using UNIF(0,1) and compared to a limit; similarly, p5 computed.
- Pt's score at V5 compared to threshold and probabilities p6, p7 and p8 computed.
- Scale results kept for visits 2,3,5,8 and endpt.

Missingness Logistics – MNAR/MNR2

- Scale results simulated for visits 2-8
- Each pt's worst score used to create distribution and threshold
- Each visit assigned a probability of being missing UNIF(0,1)
- Scale results kept for visits 2,3,5,8 and endpt for MNAR; 2, 5, 8, and endpoint for MNR2.