

Additional file 1:

Dealing with indeterminate outcomes in antimalarial drug efficacy trials: A comparison between complete case analysis, multiple imputation and inverse probability weighting

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Section A: Estimating treatment efficacy for antimalarial drugs

The primary endpoint in clinical studies of uncomplicated *Plasmodium falciparum* malaria is the occurrence of **recrudescence parasitaemia**, defined as recurrence due to the same parasite, which caused the original infection. Recrudescence occurs when the peripheral parasitaemia initially falls below the level of detection, but subsequently expands after the concentration of the antimalarial drug falls below the minimum inhibitory concentration (Figure 1). Recrudescence is the true treatment failure, since the parasite has evaded complete cure. The current approach for defining antimalarial efficacy is based on the ability of a drug to prevent the subsequent recrudescence¹. Parasite recurrence can also be due to a heterologous parasite, which can either be a **new infection** with *P. falciparum* or another species of Plasmodia during the ensuing follow-up²⁻⁴.

It is important to distinguish recrudescence from new infection so that drug efficacy attributable to parasite drug resistance can be accurately estimated. Recrudescence and new infection remain clinically indistinguishable thus necessitating usage of molecular genotyping technique, Polymerase Chain Reaction (PCR)⁵⁻⁷. The current approach for genotyping uses three polymorphic markers: merozoite surface protein (*msh*)-1, *msh*-2, and glutamate rich protein (*glurp*) genes. If at least one allele at each locus is common in pre- and post-recurrence samples, this is defined as a recrudescence, and when the alleles in the recurrent samples are different from those in the baseline samples, it is considered a new infection⁸.

When the paired analysis of pre and post treatment parasite genotypes cannot reliably determine the cause of parasitic recurrence, such outcomes are referred as “**indeterminate**”. The current WHO recommendation is to excluded the indeterminate outcomes when deriving antimalarial drug efficacy¹.

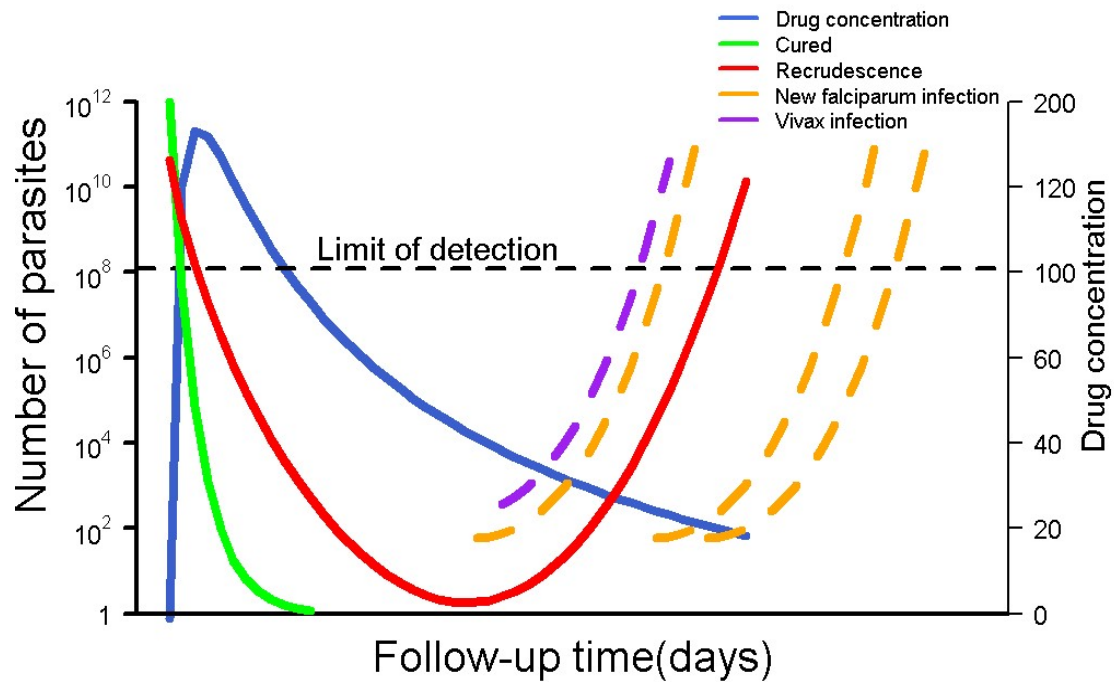


Figure 1: Therapeutic responses post antimalarial treatment in *P. falciparum* malaria.

Adapted from White NJ: The assessment of antimalarial drug efficacy. *Trends Parasitol* 2002, 18:458–464.⁹

Legend: The blue line represents a hypothetical concentration versus time profile for an antimalarial drug administered orally. The green and red lines represent scenarios for parasite burden versus time profiles following treatment for an infection where all the parasites are completely killed resulting in cure (green) and an infection where parasites are initially killed by high drug levels but with drug levels below the minimum inhibitory concentration (MIC), net parasite growth results in subsequent recrudescence (red). The purple and orange lines represent parasite-time profiles for new infections; either an infection due to a new parasite of the same species (orange) or an infection with a *Plasmodium vivax* parasite (purple) during the follow-up. The left y-axis is for parasite density, and the right y-axis shows drug levels at hypothetical units. The horizontal black line represents the microscopic limit of detection for parasites. The maximum number of parasites a human body can contain is 10^{12} .

Table 1: Risk factors associated with missing PCR outcome in the motivating dataset

	PCR outcome missing No/Yes	Odds Ratio (95% CI)	P-value
Treatment (reference=AL)	1160/29	-	-
ASAQ	909/20	0.85 [0.47-1.53]	0.585
DP	1362/13	0.39 [0.20-0.76]	0.006
Transmission (ref=High)	1687/42	-	-
Low	695/4	0.23 [0.08-0.66]	0.006
Moderate	1049/16	0.70 [0.39-1.28]	0.249

AL = artemether-lumefantrine, ASAQ = artesunate-amodiaquine, DP = dihydroartemisinin-piperaquine

Table 2: Strength of the association between variables included in the missingness model and PCR adjusted treatment failure in the motivating dataset

	Recrudescence No/Yes	Odds Ratio (95% CI)	P-value
Age in years	3369/81	0.84 [0.67-1.04]	0.108
mg/kg partner dose ^a	3369/81	0.73 [0.57-0.94]	0.013
Time of recurrence	3369/81	0.76 [0.71-0.8]	<0.001
Treatment (ref = AL)	1131/41		
ASAQ	889/18	0.70 [0.39-1.29]	0.260
DP	1349/22	0.81 [0.45-1.46]	0.495
Transmission (ref=High)	1645/57		
Moderate	1033/15	0.63 [0.34-1.16]	0.135
Low	691/9	0.63 [0.30-1.31]	0.215

^a The mg/kg dose was centred around the mean value for each partner drug

AL = artemether-lumefantrine, ASAQ = artesunate-amodiaquine, DP = dihydroartemisinin-piperaquine ; PCR= Polymerase chain reaction ; CI = Confidence Interval

Section B:

B1: Quantifying bias in complete case estimator

The following derivation are credited to Prof. Roderick Joseph Little, who generously spent time for these derivations on his peer-reviewed report of the manuscript.

Let, n be the total number of patients who were treated with an antimalarial. We define the following notations:

n_0 = number of cured patients

m_1 = number of new infections

m_2 = number of recrudescences

r = number of indeterminate outcomes

$$\Rightarrow n = (n_0 + m_1 + m_2 + r)$$

Under complete case analysis, the estimate of failure proportion is given by:

$$\hat{\rho}_{cc} = \frac{m_2}{n_0 + m_1 + m_2}$$

The bias in complete case estimator can be obtained as:

$$\widehat{Bias}_{cc} = \frac{\hat{\pi} \cdot \hat{p}_0 \cdot \hat{p}_2}{\hat{p}_0 + (1 - \hat{\pi}) \cdot \hat{p}_2 \cdot (1 - \hat{p}_0)}$$

Where $\hat{\pi} = \frac{r}{(n - n_0)}$; $\hat{p}_0 = \frac{n_0}{n}$; $\hat{p}_1 = \left(\frac{m_1}{m_1 + m_2}\right)$; $\hat{p}_2 = \left(\frac{m_2}{m_1 + m_2}\right)$

The maximum likelihood estimate of the failure proportion, under the multinomial assumption and assuming no covariates is obtained as described by Little and Rubin (2002)¹

$$\hat{\rho}_{ML} = \left(\frac{m_2}{m_1 + m_2}\right) \cdot \left(\frac{n - n_0}{n}\right)$$

¹ Little and Rubin: Chapter 13: **Models for Partially Classified Contingency Tables, Ignoring the Missing-Data Mechanism**, In Statistical Analysis with Missing Data (2002)

B2: Variance of the maximum likelihood estimator

The Large sample variance of $\hat{\rho}_{MLE}$ can be approximated following equation 13.7 from Little and Rubin (2002)²

$$\begin{aligned} Var(\hat{\rho}_{ML}) \approx & \frac{\hat{\rho}_{ML} \cdot (1 - \hat{\rho}_{ML})}{(n_0 + m_1 + m_2)} \left\{ 1 - \left(\frac{\hat{\lambda} - \hat{\rho}_{ML}}{1 - \hat{\rho}_{ML}} \right) \cdot \left(\frac{n - (n_0 + m_1 + m_2)}{n} \right) \right. \\ & \left. + \left(\left(\frac{(n_0 + m_1 + m_2) \cdot t_+}{\tau_+} \right) - 1 \right) \cdot \left(\frac{1 - \hat{\lambda}}{1 - \hat{\rho}_{ML}} \right) \right\} \end{aligned}$$

Where $\hat{\lambda}$ is the conditional probability of recrudescence given any recurrence among clearly differentiated recurrences, t_+ is the marginal probability of recurrence among all patients, and τ_+ is the overall number of clearly differentiated recurrences estimated respectively as:

$$\hat{\lambda} = \frac{m_2}{m_1 + m_2}; t_+ = \frac{m_1 + m_2 + r}{n}; \tau_+ = m_1 + m_2.$$

² Little and Rubin: Chapter 13: **Models for Partially Classified Contingency Tables, Ignoring the Missing-Data Mechanism**, In Statistical Analysis with Missing Data (2002)

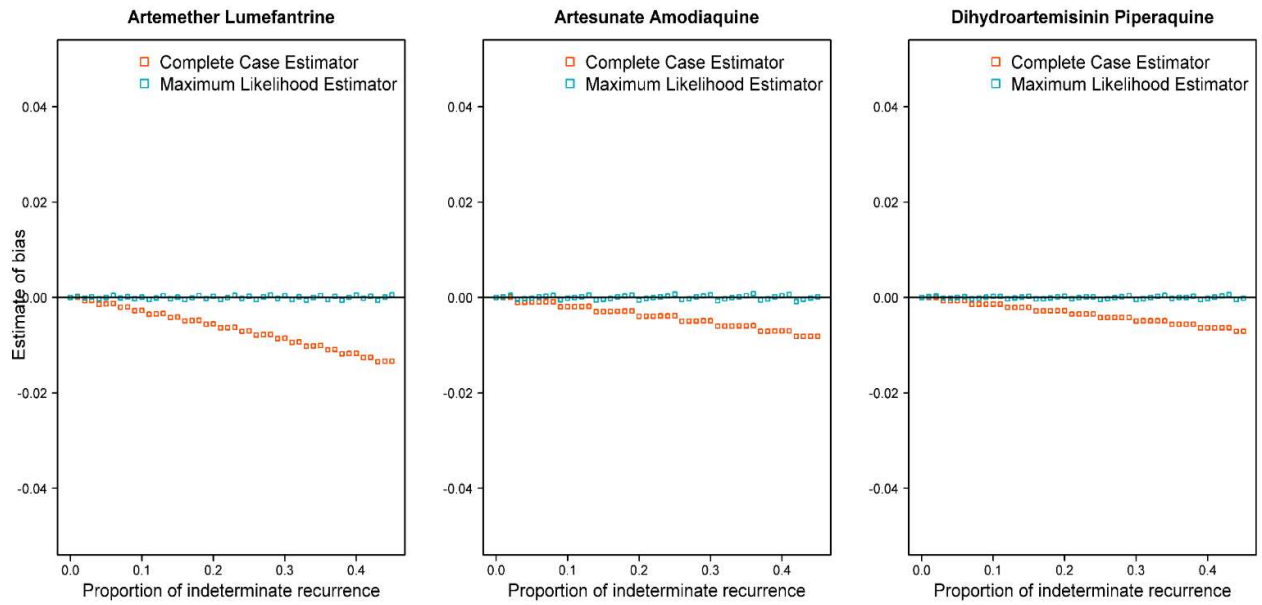


Figure 2: Theoretical estimate of bias for a given proportion of recurrences set as missing (indeterminate) under Missing At Random

Legend: The maximum likelihood estimate of the failure proportion, under the multinomial assumption and assuming no covariates

Section C: Application of Rubin's combination rules for pooling multiply imputed Kaplan-Meier estimates

With M sets of imputations, let \widehat{S}_m be the estimate of the Kaplan-Meier (K-M) survival probability for m^{th} imputation, $m=1,2,3,\dots,M$. The final survival estimate was then obtained by averaging over M imputations as $\bar{S}(t) = \sum_{m=1}^M \frac{\widehat{S}_m}{M}$. The variance of $\bar{S}(t)$ was estimated by accounting for within-imputation (W) variability and between-imputation (B) variability

$$Var(\bar{S}(t)) = W + \left(1 + \frac{1}{M}\right) B$$

Where $W = \sum_{m=1}^M \frac{w_m}{M}$; $w_j = var(\widehat{S}_m)$ and $B = \frac{1}{(M-1)} \sum_{m=1}^M (\widehat{S}_m - \bar{S}(t))^2$

An estimate of the variance of the *cloglog* transformed K-M was obtained using Taylor's series approximation given by the following expression (Collet (2015))³

$$Var\{g(X)\} \approx \left\{ \frac{dg(X)}{dX} \right\}^2 Var(X)$$

The variance of the complementary log transformed survival estimate was then obtained as:

$$\begin{aligned} Var\{\ln(-\ln(\hat{S}(t)))\} &\approx \left\{ \frac{1}{\ln(\hat{S}(t))} \right\}^2 Var(\ln(\hat{S}(t))) \\ \Rightarrow Var\{\ln(-\ln(\hat{S}(t)))\} &\approx \left\{ \frac{1}{\ln(\hat{S}(t))} \right\}^2 \frac{1}{\hat{S}(t)^2} \cdot Var(\hat{S}(t)) \end{aligned}$$

³ Collett D: *Modelling Survival Data in Medical Research, Third Edition*.p26 (Equation 2.8). (2015)

Section D: Comparison of naïve and bootstrapped standard error for inverse probability weighting approach

The following tables show the standard errors of the complementary log-log transformed Kaplan-Meier estimates derived using IPW approaches for the three treatment regimens.

The naïve estimates of standard errors were derived without incorporating uncertainty in the estimated weights. The second column is the estimate of standard error derived as the standard deviation of the Kaplan-Meier estimate across 200 bootstrap samples. The results are averaged across 1,000 simulation runs.

Table 3: Standard errors of the naïve and bootstrapped IPW estimator presented alongside the model standard error from multiple imputation approach

	10% missing			30% missing			45% missing		
	Naïve IPW	Bootstrap IPW	MI	Naïve IPW	Bootstrap IPW	MI	Naïve IPW	Bootstrap IPW	MI
AL									
M1	0.1584	0.1656	0.1654	0.1586	0.1861	0.1823	0.1593	0.2097	0.2001
M2a	0.1585	0.1661	0.1651	0.1586	0.1879	0.1848	0.1592	0.2123	0.2041
M2b	0.1585	0.1664	0.1654	0.1587	0.1889	0.1857	0.1593	0.2151	0.206
ASAQ									
M1	0.2418	0.2532	0.2505	0.2426	0.2858	0.2823	0.2450	0.3230	0.3128
M2a	0.2417	0.2527	0.2522	0.2425	0.2846	0.2802	0.2446	0.3198	0.3090
M2b	0.2415	0.2520	0.2538	0.2424	0.2826	0.2790	0.2443	0.3173	0.3095
DP									
M1	0.2178	0.2274	0.2247	0.2186	0.2542	0.2447	0.2190	0.2841	0.2667
M2a	0.2177	0.2260	0.2252	0.2182	0.2490	0.2441	0.2187	0.2754	0.2609
M2b	0.2177	0.2246	0.2218	0.2181	0.2444	0.2382	0.2187	0.2682	0.2569

AL= artemether-lumefantrine; ASAQ = artesunate-amodiaquine; DP= dihydroartemisinin-piperaquine; Naïve SEs = SEs for the IPW estimator without incorporating uncertainty in the estimated weights; Bootstrap SEs = SEs derived as the standard deviation of the Kaplan-Meier estimate across 200 bootstrap samples; SE = standard error after complementary log-log (cloglog) transformation of K-M estimate; MI = Multiple Imputation; M1 = Missingness Mechanism 1; M2a = Missingness Mechanism 2a; M2b = Missingness Mechanism 2b

Section E: Additional results on performance measures for the simulation study

Table 4: Performance measures of different approaches for handling missing outcome for artemether-lumefantrine [Full data Kaplan-Meier estimate of day 28 cure (SE) = 0.960 (0.1559)]

	10% Missing						30% missing						45% missing					
	Bias	rBias	ModSE [†]	EmpSE	CP	RMSE	Bias	rBias	ModSE [†]	EmpSE	CP	RMSE	Bias	rBias	ModSE [†]	EmpSE	CP	RMSE
M1																		
CC	0.0034	0.35	0.1672	0.1505	0.909	0.1815	0.0104	1.08	0.1905	0.1774	0.504	0.3691	0.0159	1.65	0.2152	0.2032	0.134	0.5732
IPW	0.0002	0.02	0.1656	0.1543	0.958	0.1551	0.0001	0.01	0.1861	0.1742	0.957	0.1749	0.0002	0.02	0.2097	0.2015	0.954	0.2028
MI	-0.0002	-0.02	0.1654	0.1600	0.962	0.1601	-0.0012	-0.13	0.1823	0.1707	0.961	0.1715	-0.0026	-0.27	0.2001	0.1854	0.944	0.1914
IPW-E	0.0018	0.19	0.1660	0.1544	0.946	0.1652	0.0039	0.40	0.1968	0.1867	0.903	0.2224	0.0039	0.41	0.2536	0.2582	0.851	0.2918
M2a																		
CC	0.0035	0.37	0.1676	0.1511	0.905	0.1840	0.0108	1.12	0.1920	0.1788	0.471	0.3809	0.0163	1.69	0.2176	0.2053	0.123	0.5907
IPW	0.0002	0.02	0.1661	0.1566	0.96	0.1574	0.0001	0.01	0.1879	0.1769	0.957	0.1776	0.0001	0.01	0.2123	0.2028	0.957	0.2039
MI	-0.0003	-0.04	0.1651	0.1535	0.966	0.1535	-0.0012	-0.12	0.1848	0.1846	0.947	0.1850	-0.0022	-0.23	0.2041	0.1901	0.955	0.1938
IPW-E	0.0018	0.19	0.1664	0.1571	0.947	0.1681	0.0040	0.42	0.2001	0.1910	0.893	0.2281	0.0039	0.41	0.2594	0.2680	0.837	0.3019
M2b																		
CC	0.0036	0.38	0.1679	0.1518	0.902	0.1861	0.0110	1.14	0.1928	0.1800	0.458	0.3874	0.0167	1.74	0.2200	0.2060	0.101	0.6085
IPW	0.0002	0.02	0.1664	0.1563	0.961	0.1570	0.0001	0.01	0.1889	0.1787	0.961	0.1794	0.0001	0.01	0.2151	0.2051	0.957	0.2063
MI	-0.0005	-0.05	0.1654	0.1561	0.964	0.1560	-0.0011	-0.11	0.1857	0.1741	0.954	0.1745	-0.0026	-0.27	0.2060	0.1978	0.945	0.2031
IPW-E	0.0019	0.19	0.1668	0.1568	0.946	0.1680	0.0040	0.42	0.2016	0.1927	0.894	0.2304	0.0040	0.41	0.2659	0.2772	0.831	0.3119

[†]The model based standard errors for IPW approaches were estimated using 200 bootstrap samples

M1 = Missingness Mechanism 1; M2a = Missingness Mechanism 2a; M2b = Missingness Mechanism 2b; rBias = Relative bias (%); ModSE = Model based standard error; EmpSE = Empirical standard error; CP = Coverage Probability; RMSE = Root Mean Squared Error; CC = Complete Case; IPW = Inverse probability weighting model; MI = Multiply Imputed; IPW E = IPW model which excluded recurrence as a predictor in missingness model
SE, ModSE and EmpSE are presented on complementary log-log (cloglog) scale

Table 5: Performance measures of different approaches for handling missing outcome for artesunate-amodiaquine [Full data Kaplan-Meier estimate of day 28 cure (SE) = 0.979 (0.2367)]

	10% Missing						30% missing						45% missing					
	Bias	rBias	ModSE†	EmpSE	CP	RMSE	Bias	rBias	ModSE†	EmpSE	CP	RMSE	Bias	rBias	ModSE†	EmpSE	CP	RMSE
M1																		
CC	0.0018	0.26	0.2560	0.2438	0.896	0.2716	0.0056	0.57	0.2922	0.2787	0.720	0.4469	0.0086	0.88	0.3329	0.3166	0.407	0.6594
IPW	0.0001	0.25	0.2532	0.2499	0.941	0.2519	-0.0001	-0.01	0.2858	0.2850	0.940	0.2870	0.0000	0.00	0.3230	0.3249	0.934	0.3284
MI	-0.0006	0.25	0.2505	0.2326	0.958	0.2325	-0.0012	-0.13	0.2823	0.2639	0.955	0.2649	-0.0021	-0.22	0.3128	0.2878	0.947	0.2937
IPW-E	0.0012	0.25	0.2546	0.2505	0.926	0.2647	0.0029	0.30	0.2942	0.2921	0.885	0.3470	0.0038	0.39	0.3496	0.3579	0.818	0.4405
M2a																		
CC	0.0018	0.26	0.2556	0.2442	0.897	0.2706	0.0055	0.56	0.2906	0.2774	0.725	0.4383	0.0085	0.86	0.3301	0.3154	0.437	0.6455
IPW	0.0001	0.25	0.2527	0.2490	0.946	0.2509	-0.0001	-0.01	0.2846	0.2827	0.942	0.2846	-0.0001	-0.01	0.3198	0.3241	0.931	0.3270
MI	-0.0003	0.25	0.2522	0.2418	0.959	0.2422	-0.0014	-0.15	0.2802	0.2683	0.954	0.2702	-0.0025	-0.25	0.3090	0.2929	0.934	0.3017
IPW-E	0.0011	0.25	0.2540	0.2492	0.928	0.2632	0.0029	0.29	0.2924	0.2899	0.886	0.3437	0.0037	0.37	0.3447	0.3536	0.833	0.4323
M2b																		
CC	0.0017	0.25	0.2548	0.2437	0.902	0.2679	0.0052	0.53	0.2877	0.2733	0.736	0.4224	0.0082	0.84	0.3267	0.3125	0.459	0.6277
IPW	0.0001	0.25	0.2520	0.2457	0.946	0.2475	-0.0001	-0.01	0.2826	0.2804	0.941	0.2822	-0.0001	-0.01	0.3173	0.3199	0.936	0.3226
MI	0.0000	0.25	0.2538	0.2467	0.965	0.2480	-0.0011	-0.12	0.2790	0.2533	0.965	0.2542	-0.0021	-0.21	0.3095	0.2870	0.959	0.2923
IPW-E	0.0011	0.25	0.2532	0.2459	0.930	0.2591	0.0028	0.28	0.2892	0.2868	0.891	0.3385	0.0036	0.37	0.3397	0.3457	0.837	0.4219

†The model based standard errors for IPW approaches were estimated using 200 bootstrap samples

M1 = Missingness Mechanism 1; M2a = Missingness Mechanism 2a; M2b = Missingness Mechanism 2b; rBias = Relative bias (%); ModSE = Model based standard error; EmpSE = Empirical standard error; CP = Coverage Probability; RMSE = Root Mean Squared Error; CC = Complete Case; IPW = Inverse probability weighting model; MI = Multiply Imputed; IPW E = IPW model which excluded recurrence as a predictor in missingness model
SE, ModSE and EmpSE are presented on complementary log-log (cloglog) scale

Table 6: Performance measures of different approaches for handling missing outcome for dihydroartemisinin-piperaquine [Full data Kaplan-Meier estimate of day 28 cure (SE) = 0.983 (0.2082)]

	10% Missing						30% missing						45% missing					
	Bias	rBias	ModSE†	EmpSE	CP	RMSE	Bias	rBias	ModSE†	EmpSE	CP	RMSE	Bias	rBias	ModSE†	EmpSE	CP	RMSE
M1																		
CC	0.0016	0.16	0.2296	0.2071	0.904	0.2391	0.0047	0.48	0.2618	0.2385	0.605	0.4334	0.0076	0.73	0.2997	0.2903	0.256	0.6726
IPW	0.0001	0.01	0.2274	0.2158	0.957	0.2179	0.0001	0.01	0.2542	0.2470	0.95	0.2493	0.0044	-0.01	0.2841	0.2812	0.946	0.2831
MI	-0.0003	-0.03	0.2247	0.2131	0.961	0.2131	-0.0010	-0.10	0.2447	0.2234	0.957	0.2257	0.0045	-0.15	0.2667	0.2457	0.948	0.2528
IPW-E	0.0014	0.14	0.2298	0.2156	0.923	0.2415	0.0036	0.37	0.2703	0.2635	0.766	0.3851	0.0062	0.49	0.3342	0.3490	0.601	0.5332
M2a																		
CC	0.0013	0.14	0.2276	0.2042	0.917	0.2292	0.0042	0.43	0.2562	0.2340	0.673	0.3979	0.0070	0.66	0.2882	0.2755	0.337	0.6028
IPW	0.0002	0.02	0.2260	0.2120	0.955	0.2141	0.0001	0.01	0.2490	0.2397	0.951	0.2416	0.0043	0.00	0.2754	0.2737	0.943	0.2754
MI	0.0000	0.00	0.2252	0.2064	0.972	0.2073	-0.0005	-0.05	0.2441	0.2254	0.971	0.2253	0.0042	-0.13	0.2609	0.2381	0.953	0.2432
IPW-E	0.0012	0.12	0.2281	0.2121	0.927	0.2335	0.0032	0.32	0.2626	0.2528	0.804	0.3521	0.0058	0.43	0.3208	0.3353	0.653	0.4856
M2b																		
CC	0.0011	0.11	0.2260	0.2025	0.928	0.2217	0.0037	0.38	0.2506	0.2306	0.733	0.3632	0.0064	0.60	0.2782	0.2598	0.424	0.5397
IPW	0.0002	0.02	0.2246	0.2108	0.959	0.2128	0.0001	0.01	0.2444	0.2354	0.951	0.2374	0.0041	0.00	0.2682	0.2643	0.946	0.2662
MI	-0.0003	-0.03	0.2218	0.2010	0.974	0.2009	-0.0006	-0.06	0.2382	0.2128	0.972	0.2130	0.0041	-0.10	0.2569	0.2380	0.960	0.2401
IPW-E	0.0010	0.11	0.2263	0.2103	0.933	0.2275	0.0028	0.28	0.2555	0.2462	0.830	0.3254	0.0054	0.38	0.3082	0.3178	0.709	0.4418

†The model based standard errors for IPW approaches were estimated using 200 bootstrap samples

M1 = Missingness Mechanism 1; M2a = Missingness Mechanism 2a; M2b = Missingness Mechanism 2b; rBias = Relative bias (%); ModSE = Model based standard error; EmpSE = Empirical standard error; CP = Coverage Probability; RMSE = Root Mean Squared Error; CC = Complete Case; IPW = Inverse probability weighting model; MI = Multiply Imputed; IPW E = IPW model which excluded recurrence as a predictor in missingness model
SE, ModSE and EmpSE are presented on complementary log-log (cloglog) scale

Table 7: Performance measures of different approaches for handling missing outcome for AL for estimating cured proportion [Full data estimate of day 28 cured proportion (SE) = 0.964(0.1562)]

	10% Missing						30% missing						45% missing					
M1	Bias	rBias	ModSE†	EmpSE	CP	RMSE	Bias	rBias	ModSE†	EmpSE	CP	RMSE	Bias	rBias	ModSE†	EmpSE	CP	RMSE
CC	0.2643	0.27	0.1664	0.1627	0.908	0.1857	0.8692	0.90	0.1897	0.1935	0.5770	0.3539	1.3724	1.42	0.2153	0.2177	0.2140	0.5503
MLE	-0.0002	-0.02	0.1655	0.1631	0.943	0.1632	-0.0001	-0.01	0.1866	0.1925	0.9350	0.1929	0.0000	0.00	0.2100	0.2159	0.9310	0.2169
M2a																		
CC	0.2748	0.29	0.1668	0.1637	0.909	0.1882	0.9014	0.94	0.1914	0.1977	0.5410	0.3668	1.4093	1.46	0.2179	0.2227	0.1920	0.5686
MLE	-0.0003	-0.03	0.1659	0.1636	0.944	0.1636	-0.0004	-0.04	0.1881	0.1954	0.9330	0.1954	-0.0004	-0.04	0.2123	0.2185	0.9340	0.2186
M2b																		
CC	0.2811	0.29	0.1671	0.1633	0.901	0.1888	0.9190	0.95	0.1923	0.1973	0.5300	0.3721	1.4437	1.50	0.2202	0.2248	0.1720	0.5844
MLE	-0.0004	-0.04	0.1661	0.1632	0.948	0.1631	-0.0006	-0.07	0.1888	0.1941	0.9350	0.1940	-0.0009	-0.09	0.2143	0.2204	0.9380	0.2203

M1 = Missingness Mechanism 1; M2a = Missingness Mechanism 2a; M2b = Missingness Mechanism 2b; rBias = Relative bias (%); ModSE = Model based standard error; EmpSE

= Empirical standard error; CP = Coverage Probability; RMSE = Root Mean Squared Error; CC = Complete Case; MLE = Maximum likelihood estimator of cured proportion

SE, ModSE and EmpSE are presented on complementary log-log (cloglog) scale

Table 8: Performance measures of different approaches for handling missing outcome for ASAQ for estimating cured proportion [Full data estimate of day 28 cured proportion (SE) = 0.980(0.2357)]

	10% Missing						30% missing						45% missing					
M1	Bias	rBias	ModSE ⁺	EmpSE	CP	RMSE	Bias	rBias	ModSE ⁺	EmpSE	CP	RMSE	Bias	rBias	ModSE ⁺	EmpSE	CP	RMSE
CC	0.1668	0.17	0.2563	0.2562	0.882	0.2817	0.5373	0.55	0.2951	0.3009	0.722	0.4635	0.8329	0.85	0.3393	0.3500	0.399	0.6862
MLE	-0.0001	-0.01	0.2550	0.2560	0.944	0.2573	-0.0001	-0.01	0.2907	0.3005	0.930	0.3028	0.0001	0.01	0.3320	0.3498	0.909	0.3544
M2a																		
CC	0.1591	0.16	0.2557	0.2553	0.885	0.2791	0.5198	0.53	0.2933	0.3008	0.733	0.4545	0.8105	0.83	0.3358	0.3472	0.423	0.6679
MLE	-0.0001	-0.01	0.2544	0.2548	0.939	0.2558	-0.0002	-0.02	0.2889	0.2985	0.928	0.2998	-0.0002	-0.02	0.3285	0.3450	0.922	0.3478
M2b																		
CC	0.1499	0.15	0.2549	0.2543	0.889	0.2761	0.4958	0.51	0.2907	0.3003	0.745	0.4422	0.7867	0.80	0.3321	0.3450	0.447	0.6495
MLE	-0.0002	-0.02	0.2537	0.2539	0.941	0.2546	-0.0003	-0.03	0.2865	0.2983	0.925	0.2991	-0.0004	-0.04	0.3249	0.3422	0.922	0.3436

M1 = Missingness Mechanism 1; M2a = Missingness Mechanism 2a; M2b = Missingness Mechanism 2b; rBias = Relative bias (%); ModSE = Model based standard error; EmpSE

= Empirical standard error; CP = Coverage Probability; RMSE = Root Mean Squared Error; CC = Complete Case; MLE = Maximum likelihood estimator of cured proportion

SE, ModSE and EmpSE are presented on complementary log-log (cloglog) scale

Table 9: Performance measures of different approaches for handling missing outcome for DP for estimating cured proportion [Full data estimate of day 28 cured proportion (SE) = 0.984 (0.2132)]

	10% Missing						30% missing						45% missing					
M1	Bias	rBias	ModSE [†]	EmpSE	CP	RMSE	Bias	rBias	ModSE [†]	EmpSE	CP	RMSE	Bias	rBias	ModSE [†]	EmpSE	CP	RMSE
CC	0.1630	0.17	0.2304	0.2051	0.907	0.2408	0.4718	0.48	0.2634	0.2410	0.577	0.4427	0.7094	0.721	0.3003	0.2789	0.276	0.6712
MLE	0.0001	0.01	0.2282	0.2049	0.962	0.2066	0.0001	0.01	0.2562	0.2376	0.950	0.2402	0.0002	0.020	0.2881	0.2715	0.947	0.2753
M2a																		
CC	0.1411	0.14	0.2285	0.2036	0.919	0.2319	0.4250	0.43	0.2576	0.2352	0.640	0.4054	0.6502	0.661	0.2901	0.2721	0.344	0.6104
MLE	0.0001	0.01	0.2266	0.2028	0.962	0.2042	0.0001	0.01	0.2512	0.2318	0.955	0.2340	0.0002	0.016	0.2792	0.2645	0.951	0.2677
M2b																		
CC	0.1193	0.12	0.2267	0.2027	0.926	0.2244	0.3739	0.38	0.2518	0.2316	0.708	0.3693	0.5908	0.601	0.2802	0.2584	0.407	0.5489
MLE	0.0000	0.00	0.2251	0.2021	0.959	0.2032	0.0001	0.01	0.2462	0.2285	0.955	0.2303	0.0001	0.007	0.2704	0.2524	0.957	0.2546

M1 = Missingness Mechanism 1; M2a = Missingness Mechanism 2a; M2b = Missingness Mechanism 2b; rBias = Relative bias (%); ModSE = Model based standard error; EmpSE

= Empirical standard error; CP = Coverage Probability; RMSE = Root Mean Squared Error; CC = Complete Case; MLE = Maximum likelihood estimator of cured proportion

SE, ModSE and EmpSE are presented on complementary log-log (cloglog) scale

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